McGRAW-HILL
PUBLICATIONS IN PHARMACY

Jenkins and DuMez—
QUANTITATIVE PHARMACEUTICAL CHEMISTRY

Jordan and DeKay—
QUALITATIVE ANALYSIS FOR STUDENTS OF PHARMACY AND MEDICINE

Lynn—
PHARMACEUTICAL THERAPEUTICS

Spease—
PHARMACEUTICAL MATHEMATICS

PHARMACEUTICAL THERAPEUTICS

WITH PHARMACOLOGY, POSOLOGY AND TOXICOLOGY

BY
ELDIN V. LYNN, Ph.D.
Professor of Chemistry, Massachusetts College of Pharmacy, Boston; formerly Professor of Pharmacology and Chemistry, University of Washington, College of Pharmacy, Seattle

Second Edition

McGRAW-HILL BOOK COMPANY, Inc.
NEW YORK AND LONDON
1938

COPYRIGHT, 1929, 1938, BY THE
McGRAW-HILL BOOK COMPANY, INC.

PRINTED IN THE UNITED STATES OF AMERIC

THE USE IN THIS VOLUME OF CERTAIN PORTIONS OF TH
TEXT OF THE UNITED STATES PHARMACOPOEIA IS BY VIRTU
OF PERMISSION RECEIVED FROM THE BOARD OF TRUSTEE
OF THE UNITED STATES PHARMACOPOEIAL CONVENTION. TH
SAID BOARD OF TRUSTEES IS NOT RESPONSIBLE FOR AN
INACCURACY OF QUOTATION, NOR FOR ANY ERRORS IN TH
STATEMENT OF QUANTITIES OR PERCENTAGE OF STRENGTHS

PERMISSION TO USE FOR COMMENT PARTS OF THE TEXT O
THE NATIONAL FORMULARY, SIXTH EDITION, IN THIS VOLUM
HAS BEEN GRANTED BY THE COMMITTEE ON PUBLICATIONS B
THE AUTHORITY OF THE COUNCIL OF THE AMERICAN PHARMA
CEUTICAL ASSOCIATION

THE MAPLE PRESS COMPANY, YORK, PA

PREFACE TO THE SECOND EDITION

The tremendous changes which have occurred in this field during the past nine years have necessitated a radical revision. Numerous additions and deletions were made in the United States Pharmacopœia and in the National Formulary, and many new drugs are today being used. Knowledge concerning vitamins and endocrines is progressing continuously, and what has here been recorded about them will in a short time probably be inadequate. This is also true in lesser extent of other classes of remedial agents. Nevertheless, it is believed that the facts set down are correct at present writing.

Although the same general principles have been employed as in the earlier edition, it will be noted that some rearrangement was deemed advisable. There was also a sincere attempt to alter the text in line with criticism from others. The most notable and general change has been in omitting doses of the British Pharmacopœia.

The writer would appreciate further criticisms on facts and arrangement, with the view to making this volume ultimately of maximum aid to the student in pharmacy.

E. V. LYNN.

BOSTON, MASS.,
March, 1938.

PREFACE TO THE FIRST EDITION

Up to the present time there has been available no unified text on pharmacology and toxicology for students of pharmacy. There are a number of modern and very satisfactory books on these subjects written for the medical student and practitioner, but no one has attempted to present such a field in simple manner, without the practical therapeutic applications. As a matter of fact, there has previously been little need for such a text, because the shortness of time allowed for a complete course in pharmacy had necessarily limited the amount which could be devoted to pharmacology and toxicology, and some schools even omitted any such instruction. With the advent of a minimum standard, however, requiring three years of full-time training and a probability of four years shortly, there is now time for this necessary part of a pharmacist's education. In order to give instruction accordingly, teachers must resort to various expedients. Some have preferred to place reliance on the numerous books which deal with physiological action and therapeutic uses as a part of pharmacognosy, and upon chemical texts as a basis for toxicology. Others have gone to the opposite extreme by adopting one of the excellent treatises written for medical students. Others have seen fit to do without a text.

The present volume is intended to supply the need thus presented. The author, although previously using in his classes a popular book designed for the physician, has for some time felt the lack of a good text written for the use of pharmacists, and has attempted to adapt the following pages for this purpose. Under each drug are considered its physiological actions most important in the treatment of disease and most significant in the diagnosis and treatment of poisoning. The principles of its therapeutic employment, which are very closely associated with these actions, are given in outline, without any attempt to describe the practical applications. The symptoms of toxic effects are presented, possibly more extensively than is necessary, although not too intensively for the poisons most commonly met. Finally, the average and maximum doses are stated, both in the text and as a list in the appendix. In the opinion of the writer, all of these subjects seem of primary importance to the pharmaceutical practitioner and are best studied collectively under each drug.

With the exception of arrangement, no claim can be made for originality of material contained in the text. The numerous treatises on pharmacology, on therapeutics, and on toxicology have been freely consulted, and the pharmacopœias, formulary, and dispensatories utilized as far as possible. Due appreciation of the aid thus received is here acknowledged.

The maximum doses are in most cases mean values of those given in various books and original articles. In every instance of considerable disagreement between the authorities, the final number assigned is a minimum. The doses are given, as is the universal custom, in both systems of units, but it would be preferable if we could confine ourselves to the metric or decimal system.

In order to meet the pharmacist's need, it was necessary to make comprehensive the list of described drugs. Each medical practitioner usually prescribes but a small number and naturally has his preferences, but the pharmacist must be intimately acquainted with all of the remedies which may be employed. In any one locality, all of these will probably not be called for, but the compounder must, nevertheless, be prepared at any time to dispense each or every one. With this condition in mind, there have been included all of the drugs comprised by the two pharmacopœias in the English language, by the National Formulary, by New and Nonofficial Remedies, and all besides these which experience has taught are sometimes handled in the modern drug store. In order to save space, nearly identical preparations in any of these sources have been listed under one head and assigned the title given most often in this country.

The classification adopted is one which the writer has gradually developed during an extensive teaching experience. Undoubtedly, many would be inclined to prefer one based upon pharmacological action entirely or upon therapeutic use only, but there are numerous objections to either plan, the chief of which is our ignorance of the behavior of most minor drugs. It is believed that the present method, based upon a combination of both, fits best the requirements of a dispensing pharmacist.

Careful consideration has been given to the findings of the Commonwealth study as outlined in the final report. This exhaustive investigation of the profession of pharmacy by unbiased observers has been a revelation as to the knowledge which should be possessed by prospective practitioners and well deserves high commendation. It is thought that the present text follows closely the needs of the pharmacy student as disclosed by this report.

In conclusion, the writer desires to express here his appreciation of the great assistance rendered by others. Especially is he indebted to Dr. R. A. Lyman who painstakingly examined the whole manuscript, pointing out many errors and omissions and offering several valuable suggestions. To these and to others who have extended their cooperation may be attributed a certain share of the value which might belong to this volume. The writer is deeply grateful for this assistance.

E. V. LYNN.

SEATTLE, WASHINGTON,
December, 1928.

ABBREVIATIONS

U. S. P.—United States Pharmacopœia, Eleventh Revision.

N. F.— National Formulary, Sixth Edition.

B. P.— British Pharmacopœia, 1932

N. R.— New and Nonofficial Remedies, 1938 Edition. (The American Medical Association prefers N. N. R.)

Gm.— gram or grams.

mg.— milligram or milligrams.

cc.— cubic centimeter or cubic centimeters.

CONTENTS

PAGE

PREFACE TO THE SECOND EDITION. vii

PREFACE TO THE FIRST EDITION. ix

ABBREVIATIONS. xii

INTRODUCTION 1

SUBSTANCES OF NO REMEDIAL VALUE 20
Colors, Flavors, Sweetening Agents, Solvents

ACTING LOCALLY—PROTECTIVE. 35
Demulcents, Emollients, Detergents, Emulsifiers, Dentifrices, Alimentary and Dusting Powders, Plasters, Poultices, Bandages

ACTING LOCALLY—IRRITANT. 56
Local Stimulants, Counter-Irritants, Sternutatories, Escharotics, Depilatories, Astringents

ACTING LOCALLY—ON THE CAUSE OF DISEASE 87
Antiparasitics, Anthelmintics, Antiseptics

THE ALIMENTARY TRACT 128
Intestinal Antiseptics, Antacids, Emetics, Antiemetics, Purgatives, Antidiarrheics, Cholagogues, Stomachics, Carminatives, Digestants, Nutrients, Vitamins

THE GENITO-URINARY TRACT 177
Diuretics, Urinary Antiseptics, Urinary Alkalizers and Acidifiers, Antilithics and Lithontriptics, The Reproductive Organs

THE RESPIRATORY TRACT. 197
Expectorants, Respiratory Stimulants

THE CIRCULATION 209
Digitalis Group, Circulatory Stimulants, Oxygen, Circulatory Depressants, Blood Alterations, Vasodilators and Vasoconstrictors

PAGE

THE NERVOUS SYSTEM 229

Peripheral Motor Paralyzants (Belladonna Group, Anhydrotics, General Muscular Relaxants, Bronchial Antispasmodics, Uterine Relaxants, Vasodilators), Peripheral Motor Stimulants (Epinephrine Group, Uterine Stimulants, Stimulants of Secretions), Local Anesthetics, Anesthetics, Analgesics, Antipyretics, Hypnotics, Sedatives, Central Motor Stimulants

SPECIFICS 305

Antisyphilitics, Alteratives, Antimalarials, Antirheumatics, Serums, Vaccines, Allergy, Fever Therapy, Chaulmoogra Oil

METABOLIC 354

Iron, Phosphorus, Phosphorus Compounds, Radiotherapy, Endocrines and Related Substances

IMPORTANT POISONS NOT USED AS DRUGS 376

APPENDIX 381

INDEX. 399

PHARMACEUTICAL THERAPEUTICS

INTRODUCTION

Scope of Text

The capable pharmacist, in addition to possessing a thorough knowledge of the chemical and physical properties of the substances which he handles, must also be acquainted with the *physiological action* and *therapeutical uses* of drugs. It is not intended that he know how to treat disease or that he be intimately conversant with the medical application of remedial substances. Counter prescribing is considered objectionable, not only because of possible consequences and because it endangers the spirit of cooperation between pharmacist and physician, but, also, because it is illegal. Nevertheless, an intelligent fulfillment of required duty can hardly be expected of one who combines the ingredients of a prescription unless he has an accurate, even if incomplete, knowledge of the purposes intended. The written order is often left to the pharmacist to finish, only the essential substances being designated. Knowing the object for which these are designed, he then easily makes the complete medicine. Furthermore, it may be necessary to discuss the whole situation with the physician, in which case the uninformed would be greatly at a loss. Finally, the dosage is frequently dependent upon the object attempted, and the pharmacist's prerogative of questioning an improper amount can be exercised only if he is familiar with this purpose.

In addition to these reasons, and as a partial extenuation for a certain amount of counter practice, we might quote from the report of the Commonwealth Committee.[1]

> . . . in practice customers with ailments do consult the pharmacist in their normal quest for something to ease their trouble. Undoubtedly, when

---

[1] "Basic Material for a Pharmaceutical Curriculum," p. 7, McGraw-Hill Book Company, Inc., 1927.

the pharmacist thinks he knows the cure for an ailment, he is inclined to tell the customer what to do. In time this grows into what is known as counter prescribing. This tendency to help people in distress is a very human manifestation of unselfishness, but it frequently leads the pharmacist into objectionable and dangerous practices in those cases in which he thinks he knows the nature of the disease, but does not.

The easy and summary disposition to make of this possible function of pharmacy—the dissemination of information about non-communicable diseases—is drastically to prohibit all advice upon the part of the pharmacist, and to keep him in complete ignorance of the nature of disease. A method of procedure of much greater promise, however, is to teach the pharmacist more about the nature of disease with the full expectation that when he knows more about the dangers involved, he will increasingly refuse to give advice about complex diseases. Possibly the cure for counter prescribing is not greater ignorance but more knowledge.

A fairly intimate knowledge of the toxicity of common poisons which may be taken purposely, and of the poisonous effects of other drugs accidentally ingested, must necessarily be part of the pharmacist's stock in trade. In case of such occurrences, the patient is usually seen first by him, and he must be able to meet the consequent situation. A life often depends upon promptness of treatment, minutes or even seconds being of the utmost importance. The procedure necessary in the case of an unknown poison involves a more or less correct diagnosis from the symptoms presented or at least a knowledge of the means to combat or correct the probable cause of these conditions. To function properly in this role of emergency physician, a pharmacist should be intimately conversant with the symptoms and effects caused by extraordinary doses of the drugs he handles and with remedial measures considered most adequate.

Finally, the usual and maximum doses of drugs must be quickly available to the dispenser. A carefully compiled list of these should be at hand in every drugstore which makes any pretense of filling prescriptions. The student in pharmacy ought to learn the average and the maximum doses, and it is possible to teach them only by giving exact values. It would seem best to require that each student learn thoroughly the official average and a selected maximum figure. Even if later he has not remembered the exact amount, an approximation will generally be retained in his memory, and this is the important thing. When the doses given in a prescription are too high, the fact will then be apparent to him, and the physician will be consulted. Along with a knowledge of physiological action, of therapeutical principles, and of toxic effects and treatment, we expect the capable pharmacist to be acquainted with doses which may be unsafe. These subjects will constitute the text of the present volume: pharmacology; therapeutics; toxicology; posology.

REFERENCES

The student is expected to become acquainted with the most important large reference books. No emphasis need be laid upon the significance attached to a thorough knowledge of the "United States Pharmacopœia" or of the "National Formulary" or probably also of the dispensatories. These are a necessary part of his whole training, and the importance of constant reference to them must have been repeatedly pointed out in his elementary instruction. The writer wishes to emphasize, however, that no pharmacist can be too familiar with either the pharmacopœia or the formulary; the habit of daily reading in them is a good one to form. Another book which is just as valuable, and yet so often not available, is "New and Nonofficial Remedies." This description of new or old drugs often prescribed is much more important to the pharmacist than to the physician. Revised annually by the council on pharmacy and chemistry of the American Medical Association, it contains descriptions of those non-secret remedies for which unwarranted claims are not made and which are not merely modifications of existing preparations. Theoretically, therefore, one should find here all unofficial substances not yet included in the pharmacopœia but often prescribed. Besides the volumes mentioned, the student should have for reference most of the following:

Cushny, "Pharmacology and Therapeutics," 1924
Sollmann, "Manual of Pharmacology," 1936
Solis-Cohen and Githens, "Pharmacotherapeutics," 1928
Peterson and Haines, "Legal Medicine and Toxicology," 1920
Blyth, "Poisons, Their Effects and Detection," 1920
Bastedo, "Materia Medica Pharmacology and Therapeutics," 1932

THE SUBJECT MATTER

In its broadest sense, the term **pharmacology** has been employed to mean the science which treats of drugs, including their source, chemical, physical, and physiological properties, identification, compounding, dosage, etc. Pharmacy, the art of combining remedies, is thus seen to be a subdivision, as are also pharmacognosy, identification, and the older phrase materia medica. Custom, however, has restricted this cumbersome definition to one particular phase, and we shall define pharmacology as the *study of the action of drugs upon the animal organism.* Since the physiological effect obtained is sometimes quite different in health and in disease, there is some tendency in recent years to substitute the term *pharmacodynamics* and to use pharmacology only for action under pathological conditions. Although there may be considerable justification for such change, it is not necessary for the purposes of this text, and we shall retain the word for the definition given.

Therapeutics, or therapy, is the application of remedial agents in the treatment of disease but is also often used to designate that course of study which deals with this application. Any means which may be used to counteract abnormal conditions of the body is theoretically a therapeutic agent; venesection, surgery, bonesetting, etc., are thus considered part of the whole subject. For our object, however, we may define therapeutics as *that branch of science which has to do with the use of drugs in the treatment of disease.* It is practically and closely related to the study of pharmacology. At this point, it is well to point out that there is a great distinction between the principles of therapeutics and its practice and that the pharmacist is much less concerned with the latter. We know, for example, that atropine will paralyze the myoneural junctions of parasympathetic nerves, a pharmacological observation, and we learn further that such an effect may be utilized in therapeutics to decrease nasal secretions, both of these facts being of considerable importance to the student of pharmacy. As pharmacists, however, we need go no farther, although we may be greatly interested in the practical application of this action to the treatment of coryza, etc.

Toxicology is the study of poisons, including their effects, detection, and methods of counteracting. A *poison* may be defined as *any substance which, introduced into the body in excessive amounts, causes harmful effects.* As a matter of fact, almost any material would answer this description, since even water in sufficient quantity will injure the body and has been known to cause death. It is deemed necessary by some authorities to restrict this amount in the definition; for example, Sollmann places it at 50 grams, while the Washington statutes define a poison as a substance which will destroy life in doses of 60 grains or less. The legal definition is variously expressed by different legislative bodies, but, in many cases, any quibbling over whether a certain material answers the description is prevented by appending the phrase "or anything which may be noxious or harmful." The effects of a poison on the body are obviously a portion of pharmacology, and the treatment is just as much a part of therapeutics, so that all three subjects are very intimately related; together they constitute the subject matter with which we are here concerned.

DEFINITIONS

In order to comprehend thoroughly any particular science, it is first necessary to know the technical language used, and a few fundamental definitions may be given at this point. The effect which will follow the application (*administration*) of a material to the animal body will vary with the character of that substance. Sometimes there is an alteration of tissue or reaction at the point of contact, and this we speak of as *local action.* This may take place on the skin, in the mouth, in the stomach, or at any point which can be reached by direct contact. Strictly, any portion of the body is more or less readily accessible, but we call that effect which takes place after entrance into the blood stream a *general* or *systemic action,* and any effect which is brought about within the body by contact with a certain structure after such entrance a *direct action.* The latter may influence the other tissues and organs in such a way that another result is obtained at a more distant point to which the drug itself does not penetrate. This is called an *indirect* or *remote action. Immediate* or *primary* effects occur at once; *late* or *secondary* ones follow after some time. *Side actions* are concomitant but undesirable results which may take place with or after the expected one. All of these terms are used more or less loosely by different authors, but they will be used in this volume as indicated. Some materials are readily taken into the circulation from all surfaces, while others do not penetrate under any circumstances. The process of entering the blood stream is called *absorption*. Since there is a constant tendency for the blood to get rid of foreign materials, sooner or later the absorbed drug will be thrown out by *elimination*. It may still remain in the body and may even be reabsorbed, but eventually it is discarded, the process being then termed *excretion*. During the sojourn in or on the body, the results produced may often be observed by the eye, by the ear, by means of instruments, or otherwise. These discernible effects are called *symptoms*, a term also applied to those effects observable during *pathological* (diseased) conditions. *Diagnosis* is identification of the causative agent or condition from a knowledge of these symptoms. The prediction as to the ultimate outcome expected, after treatment according to usual methods, is called *prognosis*. Quite frequently a drug is employed because experience has shown beneficial results, although the reason why they occur is obscure. This is termed an *empirical use*.

Mode of Action

The actions of drugs may be *classified* in a number of ways. Some prefer to consider only the mode of action, a view which is entirely pharmacological. Others divide the remedies used according to the effects obtained, which is the therapeutist's method of observation; while a third class of authorities would classify them in conformity with the tissue or organ affected, which is but a viewpoint of the physician. Each system has its advantages for particular purposes, but for our ends a combination of all three will best serve.

Aside from local action, most drugs are effective in but one of two ways. Whenever the substance acts at the point of application, or even afterward during a journey through the body, we may have an irritant or destructive effect upon the tissue, a protective or soothing effect, or there may be some other mechanical action. After the substance is absorbed, however, any other alteration which it can bring about is either *stimulation* or *depression*. In either case, the change may involve the normal activity of the organ in question, or it may affect the functional capacity. The distinction between these may best be illustrated by two methods of preparing an athlete for some contest. He can be put into constitutional condition by a rigid system of training, including diet, exercise, and abstinence from harmful habits, in which case his body is excellently able to withstand the abnormal strains put upon it on the day of the test. On the other hand, this same athlete could have continued with his usual mode of living up to the time appointed when, by cautious use of stimulants, he possibly could endow his body with sufficient activity to equal the demands upon it. In one way the organism is given increased functional capacity; in the other it is excited to greater activity. In one potential energy is stored, while in the other only kinetic energy is brought into play. The same methods apply also to drugs, and, as in the training for athletes, functional endowment is most desirable, since increased activity leads but to exhaustion. Unfortunately, however, most potent remedies belong to the latter class. Stimulation by drugs might be expected to give enhanced functional capacity or increased activity, but in practice they give only the heightened action. The opposite effect of depression may be likewise of either type. Here, however, it is apparent, even to the uninitiated, that lowering of vital capacity is never attempted, except under unusual circumstances, as this would be contrary to all endeavors in treating disease. In almost every instance in which it is desirable to allay or decrease any function, the aim is merely to depress, temporarily, the activity. Thus a violently beating heart would be eased by some drug which reduced its action for the time being, without permanently affecting the heart structure. The term *inhibition* is often used for the depression of organic activity.

Which portions of the body are affected by drugs? The answer to this question is that each substance which gives any effect at all has a certain degree of selection for some part or parts of the human or animal organism. Potassium salts, for example, have some depressant action upon the central nervous system, while sodium compounds have little or none. Strychnine acts mostly upon the spinal cord, and chloroform influences chiefly the brain centers. No drug, however, has this selective action in undiluted form, but all of them attack, to a greater or lesser extent, several organs or tissues. The ideal remedy for a poorly performing heart would be one which corrected the abnormality without having another action of any kind, but drugs of this sort are seldom, if ever, encountered. In general, one particular effect predominates, and the further it stands out the more valuable the substance in question.

The *mechanism* by which these changes are brought about is not known. The animal body is but a complex chemical laboratory where all possible reactions are being performed constantly, with oxidations and reductions, decompositions and combinations, hydrolyses and condensations. Any foreign material, such as a drug, will obviously alter the magnitude and direction of such reactions in a manner characteristic to each. In many cases there may be but simple chemical transformations induced by the drug, but in the majority there is very little evidence to support any statement as to the means by which the result obtained is accomplished. We may presume that the substance combines in some loose way with the protoplasm in such a manner as to alter the normal processes, a suggestion which has been elaborated in the side-chain theory of Ehrlich. He assumes that a substance, to produce abnormal physiological action, must unite with certain groups (receptors) of the cell compounds, which are essential to normal processes. After all, however, such a theory gets us no nearer a true insight into the mechanism, since up to the present we have not sufficient data to substantiate any hypothesis, and no general explanation of physiological action can be given on chemical grounds. What is needed is a more thorough knowledge of the cell and its usual changes, subjects which are engrossing the attention of thousands of investigators. Until that knowledge is gained, we can but accept the pharmacological facts without explanation.

The relation between physiological action and chemical constitution of the drug is somewhat better known. When two compounds have a very similar structure, there is generally a corresponding likeness in the changes brought about by them in the organism, although apparently slight alterations in the molecule sometimes produce comparatively large differences in physiological action. In certain series of compounds a careful study of the relation has brought out some very interesting facts, and, from these, several general conclusions have been drawn, sometimes along entirely illogical lines. The determination of the truth is proceeding rapidly in the proper way, but there is a strong tendency to deduce general statements long before the facts themselves are discovered. Viewing the whole realm of chemical compounds, we understand the pharmacology of but an insignificant few among the hundreds of thousands known; the spots which indicate where we have even imperfect knowledge are but minute dots on the whole field. We should undoubtedly accomplish most by enlarging these spots until definite and exact recognition of the function played by each group or radical is fully realized. Until then, any broad set of generalizations can but lead to confusion.

Factors Influencing Action

The amount and quality of action from the administration of drugs are dependent upon (*a*) the nature of the substance, (*b*) the susceptibility of body tissues and structures, (*c*) the quantity administered, and (*d*) the amount reaching the organ to be affected. The last is intrinsically interrelated with the other three.

That the *character of the drug* itself is a fundamentally important factor is sufficiently obvious and requires no further discussion. For the same reasons the manner in which it is prepared (dilution, impurities, etc.) is just as significant. A tincture may have an entirely different effect from that of a decoction or infusion; a saturated solution can sometimes produce marked physiological changes where a more dilute form would be inert.

As has already been stated, each drug has a *selective affinity* for certain tissues without affecting the rest of the body structures or doing so to a lesser extent. Since the protoplasms of all cells are approximately alike in composition, we could expect uniform action from any one foreign material. Practically, however, most drugs show a special action on some particular organ or set of cells, with perhaps minor effects at other locations. Therapeutically, the ideal remedy would affect only the diseased portions, but, although this object is sometimes realized, it is most usual to experience a predominating result, with one or more less important side actions. Thus digitalis, as a remedy in certain heart diseases, may also greatly irritate the gastrointestinal tract, and atropine, as a nerve-end paralyzant, at the same time causes certain disturbances in the brain. A drug may be useful for any one of its known effects provided the others are not simultaneously harmful, but as a rule only a few of these are at all valuable, and one is generally predominantly so.

The *dose*, or quantity administered, is one of the most important factors concerned in disease treatment. Its study is called *posology*. The amount given will in large measure determine the quantity reaching a particular structure, so that the conditions which influence the future effect must also establish the dose. We use the term *minimum dose* to express that quantity which will just give the effect desired; *average dose* for the amount generally prescribed to an adult; *maximum dose* for the largest safe quantity; *toxic* or *poisonous dose* for that which will probably be followed by serious untoward symptoms; and *lethal* or *fatal dose* for that which may be expected to cause death. It must be borne in mind, however, that conditions may considerably alter the effect; an amount which will bring about a certain effect in one case may be either inefficient or decidedly poisonous in another. Nevertheless, the selection of appropriate values can be made within certain limits. The pharmacopœia gives such figures for average amounts, and a list of maximum doses will be found in the appendix to this volume. These should be learned by the student as each drug is studied, especially those in the list marked with an asterisk.

FACTORS INFLUENCING DOSAGE

The quantity reaching an organ, and naturally the dose, is dependent upon a large number of conditions. Most of these are of such minor importance that they are not usually considered in practice, a few only being of enough influence to warrant more than mention.

The **age** and **sex** are important because of differences in weight, in functional peculiarities, and in constitutional resistance. Usually the question of sex is not considered, although a woman should theoretically receive a somewhat smaller dose, from one-half to four-fifths; nor is the weight of an adult deemed of sufficient practical significance. The age, however, below twenty and above sixty, is almost always considered.

In general it may be stated that *children* or *older persons* require less because of differences in weight and susceptibility. The amount to be administered to children is usually calculated in proportion to age, weight, or body surface, methods sufficiently exact for practical therapy. It should be noted, however, that the very young require even less than the calculated amount and also that these methods do not take into account differences in reactivity to some drugs. Thus, children are relatively tolerant to cathartics, atropine, alcohol, and digitalis and very susceptible to morphine. The following rules are employed:

Cowling's Rule.—Multiply the average dose by the age at next birthday and divide by the adult age, taken as twenty-four. This is the most common formula.

Clark's Rule.—Multiply the dose by the weight of the child and divide by the average adult weight, selected as 150 pounds. Clearly, this gives the most accurate result.

Young's Rule.—Multiply the age in years by the average dose and divide by the age plus twelve.

Fried's Rule (for Infants).—Divide the age in months by 150 and multiply by the average dose.

The amount for aged persons (above sixty) is generally from one-half to three-fourths of that for other adults.

The **mode of administration** is perhaps the most important factor from a practical standpoint. This can be by skin, by mucous membrane, by hypodermatic injection, etc.

Some drugs are readily absorbed through the *pores of the skin* and can thus be presented by rubbing into the latter. This is called **inunction.** The most receptive portions of the skin are the loins, axillæ, abdomen, and chest. Since the epidermis is comparatively impervious to watery solutions, and since the glandular portals are filled with fatty material, it is clear that the medicament for administration by inunction must be placed in an oily vehicle or in itself answer that description. Mercury, cod liver oil, and cocoa butter are often administered in this manner, whenever other methods are contraindicated, but with the increased popularity of hypodermic injection, inunction is rapidly falling into disuse. The chief disadvantages are the amount of time consumed, the discomfort of having smears on the body, and the uncertainty of dosage. As a matter of fact, there is today little excuse for such means of introducing a drug.

Of the mucous routes available, the most convenient, most popular, and most logical one generally is *by mouth,* or **orally.** In the majority of cases, absorption is fairly rapid, although it usually does not take place until the drug reaches the duodenum. Those substances which must be acted upon by digestion before the true medicament can be utilized, such as resins, must of course be presented orally, as well as those which are to exert their action in the alimentary tract. There are frequently great difficulties to administration by mouth, and, in some instances, medication in this way is impossible. Many drugs give rise to gastric or intestinal irritation or disturb the normal processes of digestion, while others are destroyed by the alimentary enzymes or are not absorbed in sufficient amount to give the effect desired. In such cases other routes must be employed. Finally, it should be noted that the amount of absorption from the gastro-intestinal tract is often much influenced by the absence or presence of food residues.

Rectal administration of drugs is selected whenever it is inadvisable or impossible to utilize the oral method. The absorption is sometimes quite rapid, although usually slow, and the destruction by intestinal digestion or by the liver is possibly avoided. The method is relatively easy to perform and often gives excellent results. Most substances are introduced by rectum in larger doses than by mouth, but a few of them, like strychnine, require the same or even less.

The vagina, conjunctiva, urethra, bladder, etc., are also utilized as sites for the entrance of drugs. With the exception of the bladder, absorption is rapid by each method, but, since there are generally no material advantages over oral ingestion, these routes are but rarely used in practice, except for local application.

The respiratory tract is a favorite means of rapid dosage, since absorption takes place almost immediately. In the case of gaseous remedies or easily volatile liquids, this affords a very convenient and efficient method. The total quantity of material inhaled is not so important as the concentration in the inspired air and the length of time required for complete reaction.

Hypodermic or subcutaneous injections greatly shorten the time necessary for absorption, so that they are becoming more popular with the modern physician. The term "hypodermic" was originally applied to the introduction of drugs under the epidermis by means of a hollow needle and syringe and historically and commonly refers to this method only but quite often is extended to cover all cases of needle injections. For subcutaneous administration the arm or leg is usually selected, although occasionally for massive doses the breast or back of the shoulder may be more convenient. The needle is inserted just through the skin in an oblique direction, and the contents of the syringe forcibly injected without introduction of any air. The drug is best dissolved in water or normal salt solution so that the concentration is not very high; otherwise the operation may be irritating. Needless to say, precautions must be exercised to maintain asepsis.

In recent years several other modes of injection have been found very useful. *Intramuscularly*, or deeply into a muscular tissue, such as the shoulder or hip, the drug is more rapidly absorbed than subcutaneously, and there is sometimes less irritation. The substance can also be introduced directly into the blood stream (*intravenously*) by inserting the needle point into a prominent vein. This method, because of the immediate action, is becoming almost too popular, since the indications for its use are comparatively rare. Notwithstanding that it is the quickest procedure for getting absorption, the dangers thus presented are sometimes serious, and practically there is usually less need for the increased speed than is often implied.

Subnasal, sublingual, intratracheal, intracerebral, intraspinal, intrapleural, intraperitoneal, and other methods have been suggested and used. Each of them may have advantages under special conditions, but as a rule subcutaneous administration is sufficient where the oral route is inadmissible or inadvisable.

The time of administration is of less importance but is frequently taken into account with certain classes of drugs. If the stomach is empty, the drug will be less diluted and, in consequence, will be absorbed with greater rapidity. Furthermore, the body is usually more resistant in the morning, especially to narcotics. The *season, climate,* and *temperature* are also of influence but are rarely considered.

Idiosyncrasy.—Much more than infrequently, an individual may present an unusual reaction to particular substances. While this is generally quantitative only, being the ordinary effect with different doses or an intensified one with an average amount, there may be also qualitative differences; in fact, the patient may exhibit symptoms which are not only variable in kind but even diametrically opposed to that expected. The reasons assigned for such phenomena are differences in rate of absorption, in specific constitution, in complicating diseases, or in abnormal mental conditions. Nervous persons are often subject to idiosyncrasies in drug action. Sometimes the peculiar effects may be laid to impurities in the material used.

Tolerance to the effects of a drug, or the opposite *increased susceptibility,* are often encountered as special types of idiosyncrasy. Some individuals may acquire the ability to ingest large quantities of a certain substance without undergoing the usual symptoms, or this character may be inherent or congenital. Sometimes a nationally separate group of people as a whole exhibit the peculiarities, and it is well known that some species of animals are much different from others in susceptibility to certain drugs. The acquiring of lessened effects from drugs by continued ingestion is familiar to all in the habitual use of alcohol, tobacco, cocaine, and morphine. The tolerance thus established may be due to greater functional resistance (alcohol), to decreased absorption (arsenic), to increased destruction of the drug (morphine), to more rapid excretion (atropine), or to production of antibodies (toxins). It is of interest in this connection to note that decreased sensitiveness to one material may also protect against another in the same class; one tolerant to morphine requires larger doses of anesthetics or other narcotics.

Accumulation.—If the rate of elimination for a given material is lower than that of absorption, there may be accumulation in the system. With a single dose of such a substance, this will usually have no harmful result; but where the drug is being administered continuously, it may be stored up to such an extent that it would have the effect of a much larger amount. The most common materials which tend thus to accumulate and so cause harmful effects are digitalis, arsenic, lead, and mercury. The excretion of lead is so slow that minute amounts ingested at intervals can give rise to serious poisoning.

Disease.—In attempting to remedy disease the presence of any complicating pathology must be taken into account. The most common example of this is the determination of heart action before the administration of anesthetics or narcotics generally. Pregnancy and nursing are also usually contraindications to the use of certain drugs, since many of them will be harmful to the fœtus or to the suckling child. The modern method of an exhaustive physical examination before beginning any form of treatment goes far toward eliminating any untoward action because of accompanying conditions.

Mental State.—In spite of the cynical pose often adopted toward the cults which claim remedial virtues for faith, the patients' attitude to a proposed treatment is a large factor in any benefit derived from it. In general it often appears that the will to get well will tend toward recovery. This is a matter of such common experience that it is unnecessary to discuss it to any extent. Suffice it to say that the dose of a drug can frequently be reduced if the person being treated is amenable to the expected result, while insane patients, and those who obstinately refuse to recognize any possibility of betterment, may require much more.

Diet.—It is a matter of common knowledge that the food intake is a large factor in the chances for betterment in any disease. Consequently, any prescribed measures involve a carefully organized system of diet. For similar reasons, the amount of a given remedy ordered will depend to some extent upon the character and quantity of what is eaten.

Antagonism and Synergism.—As might be expected, two drugs which have the same physiological action (**adjuvants**) are often of advantage to gain the desired effect, especially if any poisonous character of one is different in quality from that of the other; under these circumstances a combination of the two would present less danger of toxicity. In addition, there are instances in which simultaneous administration of two remedies will have a result above what either one of them could cause in any amount; in place of simply additive effects, we get summation plus a certain increment which is not yet explainable. Such drugs are called *synergists*. On the other hand, combinations of drugs which act in exactly opposite ways may have little or no physiological action because of the neutralization. Atropine, for example, paralyzes the muscle nerve ends, while pilocarpine stimulates them, so that the former will prevent action of the latter. Such substances are called *antagonists*. A similar effect can be gained if the two materials act upon different structures but still bring about opposed action. Thus atropine will prevent heart slowing by digitalis, which is accomplished through stimulation of the vagus center, although atropine counteracts this by depressing the vagus nerve ends.

General Toxicology

The frequency with which poisoning is caused by various agents, of course, gives us the logical criterion as to which of these should be studied most intensely. The table herewith is adapted from a report of the Commonwealth Committee on toxicological incidence. The figures do not represent any one period and are, therefore, not quantitative, but the relative importance of the different agents is approximately represented by them. The report is based on advices from 934 pharmacists, 55 hospitals, 20 physicians, 19 coroners, and 8 health boards. Except for alcohol, which has been the cause of poisoning in a greatly increasing number of cases during recent years, the relative order accords well with that given by the standard texts.

In general, therefore, the pharmacist needs to know the symptoms and treatment for but few poisons, say the first 50 in the list given. At the same time, however, he must learn the usual means for combating a given set of symptoms, so that a case caused by any other poison can be dealt with by him quickly and efficiently. The diagnosis is sometimes impossible and frequently very difficult, and more often than not it is necessary to begin measures promptly without determining the identity of the toxic agent.

Any method of treatment may be divided into five steps, one or more of which may be eliminated in a given case. The first involves a stopping of administration if this has been continuous. In most instances, since the poisoning is usually brought about

INCIDENCE OF POISONINGS

Substance	Number	Substance	Number
Alcohol	1235	Cantharides	10
Mercury	857	Salicylates	10
Opiates	692	Cannabis	9
Phenols	662	Bromides	9
Halogens	365	Castor bean	8
Gas	236	Eserine	8
Caustic acids, etc	211	Sulfur dioxide	8
Cyanides	179	Veratrum	7
Strychnine	166	Carbon disulfide	7
Barbital and luminal	140	Tobacco	7
Lead	92	Rhus	6
Arsenic	89	Somnos	5
Arnica	78	Marsh gas	4
Chloroform	72	Nitrous oxide	4
Belladonna	57	Hydrogen sulfide	4
Phosphorus	49	Barium	4
Food	45	Nitrates	4
Oxalic acid	41	Benzene	3
Cocaine	35	Absinthe	2
Chloral	34	Phosphorus acid	2
Ether	34	Adrenalin	2
Acetanilid	32	Alum	2
Volatile oils	32	Mustard gas	2
Zinc	26	Nitrobenzene	2
Aconite	22	Quinine	2
Paraldehyde	20	Sodium fluoride	2
Petroleum	20	Sulfonaphthol	2
Sulfonal	20	Boric acid	1
Silver	19	Adaline	1
Formaldehyde	18	Benzyl chloride	1
Copper	18	Cocculus	1
Mushrooms	17	Naphthalene	1
Larkspur	16	Phenolphthalein	1
Tartar emetic	15	Blaud's pills	1
Potassium permanganate	14	Poison hemlock	1
Croton oil	13	Pyridine	1
Nitroglycerin	12	Quinidine	1
Ergot	12	Thyroid	1
Caffeine	12	Wild parsnip	1
Strophanthus, digitalis	12	Miscellaneous	175

by a single amount or at most by but a few doses which have already ceased, this step needs no consideration. The second procedure is to give some agent, called an *antidote,* which will counteract the poison mechanically, chemically, or physiologically. An acid will be neutralized by some alkali, chlorides will precipitate silver and render it inactive, while atropine will nullify the effect of pilocarpine. Next, the stomach should be emptied by means of emetics or by the stomach tube or stomach pump, which gets rid of the excess poison that is still unabsorbed. The fourth step involves a promotion of elimination of the absorbed drug by the use of materials which will open up the body channels, such as diuretics, diaphoretics, and cathartics. Finally, the harmful effects already induced are neutralized or offset by therapeutical measures: pains and headaches by those which dull perception, weakened organs by stimulation, abrasions or inflammations by soothing agents, and delirium or convulsions by opiates or other narcotics.

Classification of Drugs Used

The system of succession employed here is based upon the physiological action which best represents the most important application. From what has been described heretofore, it is apparent that most drugs produce several actions which may affect widely differing parts of the body. The selection of any one of these as the most important is sometimes largely a matter of opinion, and this will explain deviations from other texts. Many of the drugs are used empirically or for vague purposes which are difficult to trace, in which case their placement in the present system is essentially a matter of blind choice. No one method of classification can have the property of perfection, in view of the deficiencies in our present knowledge, and there may be many objections to the plan used here. It is believed, however, that this system of division fits the needs of a pharmaceutical beginner to the best advantage.

Under each heading are given those drugs which are chiefly used for the purpose, regardless of, but in approximate order of, importance, as judged by frequency of demand. The best drug of any one class may not be described at that place at all, because of its larger employment in some other way, and will then be included in the division for which it is of the most value in medicine. Thus, morphine is perhaps the best of hypnotics, but since its chief use seems to be the abolishment of pain, the description of this drug will be found under the subject of analgesics.

The discussion of each substance follows in an approximately uniform order: the preparations used and doses; a general statement giving value, history, general composition, etc.; the physiological action, absorption, and excretion; the therapeutical uses; administration; biological assays; toxicology. In the case of rather unimportant drugs, these may all be considered in one paragraph.

SUBSTANCES OF NO DIRECT REMEDIAL VALUE

COLORS

Strictly speaking, the addition of color to a material designed for administration is not a therapeutical employment, but the psychological effect is sometimes great. To the laity perfectly colorless products do not suggest so great an effect as do those which are provided with an artistic tint, and this suggestive element is often the one impulse necessary to effect a cure. In so far as such conditions meet the purposes of treatment, we may consider coloring a therapeutic agent. The usual object sought, however, is elegance in dispensing. The colors employed will depend upon the nature of the medium, especially hydrogen-ion concentration, and upon the shade desired. Aniline dyes are very seldom used, but there is no reason why the ones permitted in foods by the Food and Drugs Act should not be more popular.

1. Cochineal

Cochineal (Coccus), U.S.P., B.P. The dried female insects, *Coccus cacti* (*Coccidæ*), enclosing the young larvæ.
Tincture of Cochineal, B.P.
Cochineal Color (Liquor Cocci), N.F.
Carmine, N.F.
Solution of Carmine, N.F.

Cochineal is a very useful coloring agent. Its principle, carminic acid, is soluble in water, alcohol, or alkalies, slightly so in ether, and insoluble in oils. Alkalies change the red to purple, while acids convert the color to reddish yellow. The material was formerly supposed to have sedative properties, but it has no known physiological action and is not now employed as a remedy.

2. Indigo

Indigo Carmine (Sodium Indigotindisulfonate), B.P. Chiefly the sodium salt, $C_{16}H_8O_2N_2(SO_3Na)_2$, of indigotindisulfonic acid.

Indigo is a blue powder or dark-purple paste, sparingly soluble in water, to which it gives a dark-blue color, and insoluble in alcohol. It is not known to have any physiological action and is used almost solely as a color for poison tablets of mercuric chloride. A 4 per cent solution (4 cc.) has been employed as a test for kidney function, but it is much less useful for this purpose than phenolsulfonphthalein.

3. Red Saunders

Red Saunders (Santalum Rubrum, Red Sanders Wood, Red Sandal Wood), U.S.P. The heart-wood of *Pterocarpus santalinus* (*Leguminosæ*).

The red coloring matter is insoluble in water but soluble in alcohol, ether, and alkaline liquids. It has no known action and is employed only for coloring alcoholic solutions. It is contained in compound tincture of lavender. U.S.P.

4. Cudbear

Cudbear (Persio), N.F. A purplish red powder prepared from species of *Rocella, Lecanora,* or other lichens (*Parmeliaceæ*).
Tincture of Cudbear, N.F.
Compound Tincture of Cudbear, N.F.

The red color is imparted to aqueous or alcoholic liquids, rendered lighter by acids, and changed to purplish red by alkalies.

5. Saffron

Saffron (Crocus), N.F. The stigma of *Crocus sativus* (*Iridaceæ*).

This drug contains an orange-red principle which is soluble in water, alcohol, or acetone to give a yellow or orange solution. It has been used to promote uterine contractions and as abortifacient, but more recent investigation has shown that it is practically non-toxic, and it is now employed only as a coloring agent.

6. Caramel

Caramel (Saccharum Ustum, Burnt Sugar Coloring), N.F. A concentrated aqueous solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark-brown mass results, a small amount of alkali or alkali carbonate being added while heating.

Caramel is a very useful color in acid or alkaline solution. It has been proposed as a substitute for sugar when the latter is contraindicated in the diet, being apparently well tolerated under such condition.

7. Amaranth

Amaranth, N.F. $C_{20}H_{11}N_2O_{11}S_3Na_3$.
Solution of Amaranth, N.F. One per cent.

It is a reddish-brown powder which dissolves in water to form a magenta-red solution.

Other Colors

Safflower (American saffron), the florets of *Carthamus tinctorius*, contains a red coloring matter, carthamin, and is used as a substitute for saffron.

Turmeric, the rhizome of *Curcuma longa*, is sometimes useful for coloring acid solutions. It is also the basis for the turmeric test for borates and is a frequent adulterant of other drugs, notably ginger.

Carotene and chlorophyl, common colors in plants, are practically non-toxic and theoretically useful for additions to medicines. They are, however, easily altered by age and other substances, being quite unreliable as coloring agents.

Many drugs are sometimes employed only to give colors to mixtures. Among these may be mentioned logwood, licorice, cannabis, hydrastis, phenolphthalein and its derivatives, and the various dyes such as methylene blue and fluorescein.

According to rules governing enforcement of the food and drugs acts, several harmless aniline dyes may be used in foods, provided they do not conceal inferiority. Since these were selected because inert, there is no reason why they should not be used in drugs. The list includes amaranth, indigo, ponceau 3R, erythrosine, tartrazine, yellow OB, yellow AB, light-green SF yellowish, guinea green B, fast green FCF, naphthol yellow S, sunset yellow FCF, ponceau SX, orange I, and brilliant blue FCF.

Several artificial dyes which might be employed as colors are applied as antiseptics or for diagnosis and will be considered as a group later. Eosin, gentian violet (methyl rosaniline), congo red, neutral red, and rose bengal might be mentioned.

FLAVORS

As with colors, the addition of flavoring agents to medicinals is not exactly a therapeutic measure but is often of material aid in attaining the effect desired. Substances which are offensive to the sense of taste or smell may be rendered more inviting by adding some drug which has a pleasant aroma. Frequently the patient refuses to take obnoxious remedies and may even resort to subterfuge in order to avoid the necessity of an effective dose. Furthermore, it is often possible to select a flavoring material which will be an adjuvant to the principal drug and will thus aid in the treatment. Rightly chosen flavors are sometimes of great assistance in bringing about rapid and complete absorption, and many of them are stimulants to the processes of digestion, as well as efficient carminatives.

The list of substances employed as flavors is much longer than necessary, partly because of long-established custom and partly to satisfy individual tastes and fancies. In practice a few aromatics would undoubtedly suffice, but each physician has his own particular preferences, so that our pharmacopœias include a large number. Most of them are volatile oils, but there are also included the materials commonly called spices, the sweetening agents, a few substances which appeal to the taste without being volatile, the mucilaginous drugs, and those which paralyze the taste buds. The aromatic waters and the simple elixirs are among the most popular.

1. Orange

Bitter Orange Peel, U.S.P., B.P. The dried rind of the unripe fruit of *Citrus Aurantium* (*Rutaceæ*).

Fresh Bitter Orange Peel (Aurantii Cortex Recens), B.P.

Tincture of Bitter Orange Peel, U.S.P. Dose: 4 cc., 1 fluidrachm.

Oil of Bitter Orange, N.F. Dose: 0.1 cc., 1½ minims.

Elixir of Bitter Orange (Elixir Curassao), N.F.

Infusion of Orange Peel, B.P.

Tincture of Orange, B.P.

Syrup of Orange, B.P.

Sweet Orange Peel, U.S.P. The fresh, outer rind of the ripe fruit of *Citrus Aurantium* var. *sinensis* (*Rutaceæ*).

Tincture of Sweet Orange Peel, U.S.P. Dose: 4 cc., 1 fluidrachm.

Syrup of Orange, U.S.P.

Oil of Orange (Oil of Sweet Orange), U.S.P. Dose: 0.1 cc., 1½ minims.

Compound Spirit of Orange, U.S.P.

Aromatic Elixir (Simple Elixir), U.S.P.

Red Aromatic Elixir (Red Elixir), N.F.

Orange Flower Water, U.S.P. A saturated solution of the odoriferous principles of the flowers of *Citrus Aurantium* (*Rutaceæ*), prepared by distilling the fresh flowers with water and separating the clear, saturated portion of the distillate.

Syrup of Orange Flowers, U.S.P.
Oil of Orange Flowers (Oil of Neroli), N.F.
Iso-alcoholic Elixir, N.F.
Aqueous Elixir, N.F.

Bitter orange contains hesperidin which has a very bitter taste and indicates use of the preparations as stomachic tonics. The oils are all similar to other volatile oils in action and might be used in the same way. Orange juice is of great value as a source of vitamins (which see) for infants and invalids and as a remedy in scurvy. The orange preparations, however, are employed chiefly for flavoring purposes.

2. Lemon

Lemon Peel, U.S.P., B.P. The outer yellow rind of the fresh ripe fruit of *Citrus medica* var. *Limon* (*Rutaceæ*).

Tincture of Lemon, U.S.P., B.P.
Oil of Lemon, U.S.P., B.P. Dose: 0.1 cc., 1½ minims, U.S.P.
Syrup of Lemon, B.P.

Lemon peel contains a glucoside hesperidin, which is probably utilizable as a stomachic, and the oil is similar in action to other volatile oils, but the preparations of lemon are but rarely employed except as flavors. The juices of lime, lemon, and orange contain citric acid, which gives a pleasing taste to beverages made from them, and vitamins that are of value in scurvy and for infant and invalid feeding.

3. Cinnamon

Cinnamon, U.S.P., B.P. The dried bark of *Cinnamomum Loureirii* (*Lauraceæ*) (*C. zeylanicum*, B.P.).

Oil of Cinnamon (Oil of Cassia), U.S.P., B.P. The volatile oil distilled from the leaves and twigs of *Cinnamomum Cassia* (*Lauraceæ*). Dose: 0.1 cc., 1½ minims, U.S.P.

Cinnamon Water, U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.
Concentrated Cinnamon Water, B.P.
Spirit of Cinnamon, U.S.P. Dose: 1 cc., 15 minims.
Tincture of Cinnamon, N.F. Dose: 1 cc., 15 minims.
Aromatic Powder, N.F. Dose: 1 Gm., 15 grains.
Syrup of Cinnamon, N.F.

Oil of cinnamon is employed by the dentist as an antiseptic and local anodyne, but the principal use of the drug and its preparations is as flavor and carminative. The tannin content makes it an adjuvant to astringents.

4. Rose

Rose (Red-rose Petals, Rosa Gallica), N.F. The dried petals of *Rosa gallica* (*Rosaceæ*), collected just before the expansion of the flowers.

Fluidextract of Rose, N.F. Dose: 2 cc., 30 minims.

Oil of Rose (Otto of Rose), U.S.P. Distilled from the fresh flowers of *Rosa damascena, R. gallica,* and varieties.

Stronger Rose Water, U.S.P. A saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* (*Rosaceæ*), prepared by distilling the fresh flowers with water and separating the clear saturated portion of the distillate.

Rose Water, U.S.P.

Ointment of Rose Water (Cold Cream), U.S.P.

5. Cardamom

Cardamom Seed, U.S.P., B.P. The dried ripe seed of *Elettaria Cardamomum* (*Zingiberaceæ*), recently removed from the capsules. Dose: 1 Gm., 15 grains, U.S.P.

Compound Tincture of Cardamom, U.S.P., B.P. Dose: 4 cc., 1 fluidrachm, U.S.P.

Oil of Cardamom, N.F.

Compound Spirit of Cardamom, N.F.

Compound Elixir of Cardamom, N.F.

The preparations of cardamom are much used as flavors, as stomachics, and as carminatives, being useful adjuvants to purgatives to prevent griping.

6. Anise and Fennel

Anise (Anise Fruit), N.F. The dried ripe fruit of *Pimpinella Anisum* (*Umbelliferæ*). Dose: 0.5 Gm., 8 grains.

Oil of Anise, U.S.P., B.P. The volatile oil distilled from anise or from the dried ripe fruit of *Illicium verum* (*Magnoliaceæ*). Dose: 0.1 cc., 1½ minims, U.S.P.

Anise Water, U.S.P. Dose: 15 cc., 4 fluidrachms.

Spirit of Anise, U.S.P. Dose: 1 cc., 15 minims.

Anethol, N.F. The methyl ether, $C_6H_4 \cdot (C_3H_5) \cdot OCH_3$, of para-propenyl phenol. Dose: 0.1 cc., 1½ minims.

Fennel (Fennel Fruit, Fœniculum), N.F., B.P. The dried, ripe fruit of cultivated varieties of *Fœniculum vulgare* (*Umbelliferæ*). Dose: 1 Gm., 15 grains, N.F.

Oil of Fennel, U.S.P. Dose: 0.1 cc., 1½ minims.

Fennel Water, U.S.P. Dose: 15 cc., 4 fluidrachms.

Anise and fennel and their preparations are employed chiefly as flavoring materials, although the oils have the action of other volatile oils. They are frequently prescribed as carminatives in colic, especially for children, and as agreeable expectorants in cough mixtures. Fennel oil has attained considerable reputation in folk medicine as an emmenagogue, diuretic, galactagogue, and diaphoretic, but it is presumably no more efficient than the liquid with which it is administered. Fenchone, one of its components, is sometimes employed as a counter-irritant, either alone or diluted with alcohol or oil.

7. Clove and Pimenta

Clove, U.S.P., B.P. The dried flower-buds of *Caryophyllus aromaticus* (*Myrtaceæ*). Dose: 0.25 Gm., 4 grains, U.S.P.

Oil of Clove, U.S.P., B.P. Dose: 0.1 cc., 1½ minims, U.S.P.

Eugenol, U.S.P. A phenol, $C_6H_3(C_3H_5)(OCH_3)OH$ 1:3:4, obtained from clove and other sources. Dose: 0.1 cc., 1½ minims.

Infusion of Cloves, B.P. (Fresh and concentrated.)

Oil of Pimenta, N.F. A volatile oil distilled from the ripe fruit of *P. officinalis* (*Myrtaceæ*). Dose: 0.1 cc., 1½ minims.

Oil of Myrcia (Oil of Bay), N.F. A volatile oil distilled from the leaves of *Pimenta acris* (*Myrtaceæ*).

Compound Spirit of Myrcia, N.F.

Clove is a popular flavor and carminative, as well as a household spice. The oil is a fairly strong antiseptic and an efficient local anodyne, being employed in dentistry to relieve pain and disinfect carious teeth. It is also considered a useful ingredient of liniments. Pimenta and bay, which contain eugenol, are similar to clove, being used for the same purposes to a much smaller extent.

8. Nutmeg

Myristica (Nutmeg), U.S.P., B.P. The dried ripe seed of *M. fragrans* (*Myristicaceæ*). Dose: 0.5 Gm., 8 grains, U.S.P.

Oil of Myristica (Oil of Nutmeg), U.S.P., B.P. Dose: 0.03 cc., ½ minim, U.S.P.

Nutmeg and *mace* are much more poisonous than most other drugs containing volatile oils, and this, coupled with the former reputation of nutmeg as abortifacient, has resulted in severe cases of poisoning. The effects are mainly narcotic, with some local irritation. At present, the preparations are used as carminatives and flavors, occasionally, as in the case of clove oil, as local anodynes. Nutmeg oil is also sometimes employed as a topical agent for ringworm.

9. Sassafras

Sassafras, N.F. The dried bark of the root of *S. variifolium* (*Lauraceæ*). Dose: 10 Gm., 2½ drachms.

Oil of Sassafras, U.S.P. Dose: 0.1 cc., 1½ minims.

The oil is frequently added to mixtures as flavor and carminative and to aid other remedies in the combating of parasites.

10. Caraway and Dill

Caraway, U.S.P., B.P. The dried ripe fruit of *Carum Carvi* (*Umbelliferæ*). Dose: 1 Gm., 15 grains, U.S.P.

Oil of Caraway, N.F., B.P. Dose: 0.1 cc., 1½ minims, N.F.

Dill Fruit (Anethi Fructus), B.P. The dried ripe fruit of *Anethum graveolens.*

Oil of Dill, B.P.

Dill Water, B.P. (Concentrated and dilute.)

These preparations are used in medicine for flavoring or as adjuvants to other carminatives and correctives.

11. Lavender

Oil of Lavender, U.S.P., B.P. The volatile oil distilled from the fresh flowering tops of *Lavendula spica* (*L. officinalis, L. vera*) (*Labiatæ*). Dose: 0.1 cc., 1½ minims, U.S.P.

Spirit of Lavender, U.S.P. Dose: 2 cc., 30 minims.

Compound Tincture of Lavender (Compound Spirit of Lavender), U.S.P. Dose: 2 cc., 30 minims.

The lavender preparations are considered useful flavoring and carminative agents and are sometimes employed to produce gastric, reflex stimulation.

12. Raspberry and Cherry

Raspberry, N.F. The fresh ripe fruit of varieties of *Rubus Idaeus* or of *R. strigosus* (*Rosaceæ*).

Syrup of Raspberry, N.F.

Cherry (Sour Cherry), N.F. The fresh, ripe fruit of cultivated varieties of *Prunus cerasus* (*Rosaceæ*).

Syrup of Cherry, N.F.

13. Rosemary

Oil of Rosemary U.S.P., B.P. The volatile oil distilled from the fresh flowering tops of *Rosemarinus officinalis* (*Labiatæ*). Dose: 0.1 cc., 1½ minims, U.S.P.

Rosemary oil was formerly very popular as a rubefacient and antiparasitic but is now used but rarely for flavoring and in colic. It is often added to insecticides because the odor seems to be disagreeable to insects.

14. Coriander

Coriander, N.F., B.P. The dried ripe fruit of *Coriandrum sativum* (*Umbelliferæ*). Dose: 2 Gm., 30 grains, N.F.

Oil of Coriander, U.S.P., B.P. Dose: 0.1 cc., 1½ minims, U.S.P.

15. Bergamot

Oil of Bergamot, N.F. A volatile oil obtained by expression from the rind of the fresh fruit of *Citrus Aurantium* var. *Bergamia* (*Rutaceæ*).

Perfumed Spirit (Aqua Coloniensis), N.F.

16. Citric and Tartaric Acids

Citric Acid, U.S.P., B.P. $C_3H_4(OH)(COOH)_3 \cdot H_2O$.

Syrup of Citric Acid, U.S.P.

Tartaric Acid, U.S.P., B.P. $C_2H_2(OH)_2(COOH)_2$.

Citric and tartaric acids have in mild form the actions of other weak acids, which will be referred to later. They are employed principally, however, for flavoring and as refreshing drinks in fever. An artificial lemonade may be prepared by dissolving 2 to 3 grains of the acid in a liter of water and adding enough sugar and oil of lemon to suit the taste. For effervescent draughts, the use of carbonates converts the acids to salts, which are frequently employed in medicine and which will be discussed at the appropriate place. Citric acid has been recommended in scurvy, because lemon juice which is its source is an efficient remedy, but the knowledge of vitamins has shown this reasoning to be fallacious.

Tartaric acid is cheaper and may be used for the same purposes, although large doses may cause considerable gastric irritation. Most of it is destroyed in the alimentary tract, the rest appearing in the urine. After injection, it is eliminated by the kidneys, whereas citric acid is almost completely oxidized. In cases of poisoning, chalk or lime is the best antidote, while alkalies should be avoided.

17. Benzaldehyde

Benzaldehyde, N.F. $C_6H_5{\cdot}CHO$. Dose: 0.03 cc., ½ minim.

This compound is contained in oil of bitter almonds but is usually prepared artificially from toluene. It is dissolved by most solvents in sufficient amount to give the odor of almond. Locally it paralyzes the nerve endings and is a muscle-depressant and local anesthetic, but the ease with which it is converted by air to benzoic acid limits its employment for these purposes, and it is used mostly as a flavor.

18. Vanilla

Vanilla, N.F. The cured, full-grown, unripe fruit of *V. planifolia* (*Orchidaceæ*).

Tincture of Vanilla, N.F.

Vanillin, U.S.P. Methylprotocatechuic aldehyde, $C_6H_3{\cdot}CHO{\cdot}OCH_3{\cdot}OH$ 1:2:4.

Compound Elixir of Vanillin, N.F.

Compound Spirit of Vanillin, N.F.

Vanillin is a very mild irritant but is therapeutically valueless except as a flavor. It has been used as a sedative to the nervous system.

19. Coumarin

Coumarin (Cumarin), N.F. The anhydride, $C_6H_4(CH)_2OCO$, of ortho-oxycinnamic acid.

The odor of coumarin is very similar to that of vanillin for which it is often used as a substitute or adulterant. Although investigations have failed to find any physiological action, the drug is claimed to be sedative in whooping cough and other spasmodic conditions, and local application is said to relieve pain.

Other Flavors

Besides the foregoing, there may be occasional calls for unofficial oils, such as those of *erigeron, jasmine, rue, origanum,* etc., and for fresh fruits like *blackberry.* Carbonation is also a means of flavoring medicines. In addition, many drugs are excellent aromatics; a complete list of these will not be given here, but mention might be made of the mints, wintergreen, ginger, the balsams, licorice, ethyl acetate, almond, and eriodictyon.

SWEETENING AGENTS

What has been said about flavors in general applies also to those materials which are known as sweeteners. They are employed to disguise acrid tastes and for flavoring generally. Most of them belong to the class of sugars, but during recent years many synthetic compounds have been introduced. Attempts to link the character of chemical structure with sweetness have not been very successful. The only one which is now very popular is saccharin, formerly known as gluside or benzosulfinide.

1. Sugar

Sucrose (Refined Sugar, Saccharum, Sugar), U.S.P., B.P. A sugar obtained from *Saccharum officinarum* (*Gramineæ*), *Beta maritima* (*Chenopodiaceæ*), and other sources.

Syrup, U.S.P., B.P.

Sucrose and syrup are sweeteners for flavoring or diluting a variety of mixtures and may be used to suspend insoluble powders. The value as a nutrient is well known, and for this purpose it is sometimes administered by rectum (drip method). It is a time-honored healer for ulcers and wounds, where it exerts some local stimulant and germicidal effect; its antiseptic value is well illustrated in the preservation of foods. With the advent of modern antiseptics, the use of sugar for this purpose has been almost abandoned. In an emergency, it may serve well as a styptic or hemostatic, while most cough mixtures contain syrup as a demulcent expectorant and flavor.

2. Lactose

Lactose (Milk Sugar, Saccharum Lactis), U.S.P., B.P. A sugar, $C_{12}H_{22}O_{11}\cdot H_2O$, obtained from milk.

Betalactose, N.R. $C_{12}H_{22}O_{11}$. Crystallized above 93°C.

Lactose has only a slightly sweet taste, but it is employed largely for diluting powders because of this, and because its hardness serves to facilitate comminution. Administered internally, it has a high nutrient value, and, although it cannot alter the intestinal flora as is sometimes claimed, it is the logical sugar for modifying infants' foods.

3. Honey

Honey (Mel, Clarified Honey), U.S.P., B.P. A saccharine secretion deposited in the honeycomb by the bee, *Apis mellifera* (*Apidæ*).

Oxymel, B.P.

Honey is used to impart flavor and a sweet taste to various preparations. It has a mild laxative action and may be prescribed in the diet for this purpose. It is often added to gargles as a demulcent.

4. Dextrose

Glucose, U.S.P., B.P. A product obtained by the incomplete hydrolysis of starch. It consists chiefly of dextrose, maltose, dextrins, and water.

Syrup of Glucose, B.P.

Dextrose (d-glucose), U.S.P., B.P. A sugar, $C_6H_{12}O_6 \cdot H_2O$, usually obtained by the hydrolysis of starch.

Ampuls of Dextrose, N.F. Dose: 50 cc. (about 25 Gm.)

Ampuls of Dextrose and Sodium Chloride, N.F. Dose: 10 cc. (about 2.5 Gm. of dextrose and 1.5 Gm. of sodium chloride).

Isotonic Solution of Dextrose and Sodium Chloride, N.F. Dose: intravenous 1000 cc.

Dextrose is the normal sugar of the blood and presumably the most efficient for feeding. For such a purpose, it may be administered by mouth, by hypodermic injection, or even by rectum, although efficacy of the last is debated. It not only supplies food but also sustains the volume of blood and causes some diuresis. During recent years the intravenous injection of isotonic (5 to 6 per cent) or hypertonic (10 to 50 per cent) solutions has become very popular in a great variety of conditions. Although it can have no direct influence on micro-organisms, many of the infections yield remarkably after such injections. Its use as a supportive measure often seems lifesaving, especially in threatened death from shock after accidents or operation and in such serious conditions as broncho-pneumonia, encephalitis, eclampsia, and other toxemias. Besides, dextrose is injected to reduce the coagulation time of the blood, with insulin in psychoneuroses and in under-nutrition, in cardiac, renal, and hepatic disturbances, in poisonings of various kinds, and especially in threatened dehydration. It has even been used with alleged benefits in rheumatism, heart disease, asthma, jaundice, etc.

As a sclerosing injection for varicose veins, etc., dextrose is considered by many the best agent available.

Altogether, this sugar is fast becoming one of the most used of all drugs.

Commercial glucose, a mixture with maltose and dextrin, can replace sucrose for feeding or flavoring, although it is not so sweet. Formerly there was a prejudice against such an artificial food, but we now know that amounts equivalent to total carbohydrate can be ingested without bad effects. Manufacturers claim for it some laxative action and recommend it in the constipation of infants.

5. Levulose and Galactose

Lævulose (Fructose), B.P. $C_6H_{12}O_6$.
Solution of Invert Sugar, N.R. Obtained by the hydrolysis of sucrose.

Levulose, or fruit sugar, was at one time presumed to present an advantage as food in diabetes, in that it could be assimilated where dextrose could not. Critical observations show that it is first assimilated but later gives hyperglycemia and glycosuria, and the majority seem to think that it behaves like dextrose in metabolism, ultimately forming a substance indistinguishable from glycogen. The claims for inulin, which forms levulose on hydrolysis, and for Jerusalem artichokes, which contain inulin in place of starch, cannot be said to have been proved. Large amounts of inulin in the diet are said to give alimentary distress.

Galactose, the monosaccharide from lactose, has also been proposed in the diabetic diet, but 40 grams daily by mouth has been found to cause definite lesions in the liver and to give hyperglycemia and glycosuria. The probabilities are that it is no different from dextrose or levulose. The same might be said of salabrose and of sorbitol (sia-sugar or sionon) which have been suggested. Galactose is considered useful as a diagnostic agent.

Recently the pentoses, especially xylose, have been proposed as replacement of sugar in the diabetic diet, but experiments seem to indicate that they are not utilized in metabolism.

6. Saccharin

Saccharin (Gluside, Benzosulfinide), U.S.P. The anhydride, $C_6H_4{\cdot}CO{\cdot}SO_2{\cdot}NH$ 1:2, of ortho-sulfamido-benzoic acid. Dose: 0.03 Gm., ½ grain, in the proportion of 0.1 Gm. per liter or ½0 grain per ounce.

Soluble Saccharin (Sodium Benzosulfinide), U.S.P., B.P. Dose: as for saccharin, U.S.P.

Saccharin, or its more soluble salt, is many times as sweet as sucrose. Although use in foods is prohibited by the Food and Drugs Act, its toxicity is very low, and small doses over long periods have apparently no harmful effect. When sugar is contraindicated in the diet, as in diabetes, saccharin may be used to replace it. The taste is objectionable to some, and sugar-eating insects will not touch it.

SOLVENTS

1. Acetone

Acetone, U.S.P., B.P. Dimethylketone, $CH_3{\cdot}CO{\cdot}CH_3$.

Acetone is an excellent solvent for a variety of materials such as resins and fats and is used almost exclusively for that purpose. Administered to animals, it has a narcotic action with an especially poisonous effect on the respiratory center. It is infrequently employed as expectorant and antispasmodic, also to sterilize the hands or the site of an operation. It was once suggested as an anesthetic and later as an anthelmintic.

2. Benzin

Purified Petroleum Benzin (Petroleum Ether, Ligroin), U.S.P. A purified distillate from American petroleum, consisting of methane hydrocarbons.

Benzin is a good solvent for fats and oils and used almost entirely as such. Sometimes it is prescribed as counter-irritant in neuralgia, as an antiparasitic for lice, and as anthelmintic for the tapeworm. All petroleum products are of toxicological interest, which will be mentioned later.

3. Isopropyl Alcohol

Isopropyl Alcohol (Isopropanol), N.R. Propanol-2 $CH_3{\cdot}CHOH{\cdot}CH_3$.

Isopropyl alcohol was introduced as a substitute for ethyl alcohol. It is somewhat more toxic and should not be taken internally. It is a convenient solvent for creosote in the treatment of burns caused by this and is also mildly antiseptic.

Other Solvents

It would present no good purpose to give here a list of all those substances which are employed as solvents. Among the official substances might be mentioned alcohol, water, glycerin, ether, chloroform, oils, acetic acid, carbon tetrachloride, trichlorethylene, and petrolatum.

ACTING LOCALLY—PROTECTIVE

A large proportion of all remedies act locally, but for convenience some of them are discussed under other heads. In the present classification we have included three subdivisions: the protectives; the irritants; those acting on the cause of disease. Some of the purgatives belong in the second group, but their consideration is postponed until those are taken up which act upon the gastro-intestinal tract. Many of the bacteria are combated by substances which act after absorption, and these are, also, to be discussed later.

The protectives are used externally or internally to cover the parts to which they are applied and, in many cases, to soften and relax the tissue. Some are mere mechanical coverings, while others alter the character of cells in greater or lesser degree. They are divided into demulcents, emollients, dusting and alimentary powders, plasters, poultices, and bandages. For convenience, the dentifrices have been added.

Demulcents

The demulcents are mucilaginous substances and other colloids which have the property of forming with water viscid mixtures or pseudosolutions. They are insoluble in alcohol and hence incompatible with alcoholic solutions. The action is mechanical and purely local, although this is said to extend into the bronchi, even after oral administration. They soften and relax the tissues, soothing the parts, and therapeutically may be defined as *drugs which are applied to mucous membranes to soften, relax, and protect.* They also have great cohesive character and readily surround other matter to isolate it from outside influence.

The demulcents are *used in medicine* for a number of purposes. In pharmacy they render pill and tablet masses cohesive and aid in the suspension of insoluble powders and oils. Objectionable tastes may be disguised to some extent, as can easily be demonstrated by the greater sweetness of syrup compared to an equal amount of sugar dissolved in mucilage. The excessive acidity of a fruit is often hidden by natural demulcents, so that one cannot always estimate the amount of acid by the degree of sourness. In the same way, sensibility to temperature, irritants, and pain may be diminished considerably; a salt solution applied to an open wound will cause much greater irritation than if the salt were dissolved in starch paste. A protection can thus be afforded to inflamed or abraded surfaces against destructive poisons and even bacteria, and the demulcents are much used in bronchitis, tonsilitis, diarrhea, gastritis, enteritis, etc. In the case of infectious diseases, however, the mucilages are objectionable because they are excellent media for the growth of bacteria, and at the same time their decomposition furnishes irritant compounds.

The surrounding of particles of other matter is also utilized in *retarding absorption or elimination* of drugs. Purgatives and anthelmintics, which are to act in the lower bowel, are delayed in exerting the effect, until arrival there, by simultaneous administration of demulcents, while the rapid elimination of sodium chloride, after intravenous injection for blood replacement, is diminished by using acacia.

The demulcents may be employed in the form of lozenges for the mouth and throat or liquids for oral or rectal administration. The imbibition of large quantities of liquid is sometimes facilitated by making it more palatable with such a substance as starch or barley water, while in nutritional enemata the addition of starch serves to prevent excessive irritation.

1. Licorice

Glycyrrhiza (Licorice or Liquorice Root), U.S.P., B.P. The dried rhizome and roots of *G. glabra* var. *typica*, known in commerce as Spanish Licorice, or of *G. glabra* var. *glandulifera*, known in commerce as Russian Licorice, or of other varieties of *G. glabra* yielding a yellow and sweet wood (*Leguminosæ*). Dose: 2 Gm., 30 grains, U.S.P.

Fluidextract of Glycyrrhiza, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Extract of Glycyrrhiza, U.S.P., B.P.

Pure Extract of Glycyrrhiza, U.S.P.

Compound Powder of Glycyrrhiza, B.P.

Elixir of Glycyrrhiza (Adjuvant Elixir), U.S.P.
Syrup of Glycyrrhiza, N.F. Dose: 8 cc., 2 fluidrachms.

Licorice is a very popular demulcent and flavoring agent for expectorants, laxatives, quinine, etc. It is somewhat aperient but is usually administered with more efficient drugs, as in the compound powder with sulfur and senna. The glucoside which gives licorice its sweet taste is really a saponin but lacks the large toxicity of this class. It has no advantage over the drug and its extracts.

2. Acacia and Tragacanth

Acacia (Gum Arabic, Gum Acacia), U.S.P., B.P. The dried gummy exudation from the stems and branches of *A. Senegal* or of some other species of *Acacia* (*Leguminosæ*).

Mucilage of Acacia, U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.
Syrup of Acacia, N.F.
Injection of Sodium Chloride and Acacia, B.P.

Tragacanth, U.S.P., B.P. The dried gummy exudation from *Astragalus gummifer* or other Asiatic species of *Astragalus* (*Leguminosæ*).

Mucilage of Tragacanth, U.S.P., B.P.
Glycerite of Tragacanth, N.F.
Compound Powder of Tragacanth, B.P.

Gum arabic is employed in the manufacture of mucilages and emulsions and to suspend insoluble powders. The syrup effectively masks acrid tastes and can be mixed with other demulcent expectorants in cough and bronchitis. Acacia ferments very readily, and its nutrient value is quite low, so that the applications in therapy are limited. Solutions of 5 to 6 per cent, usually in physiological salt solution, have been used in intravenous injections to prevent shock and collapse and to replace blood. In spite of several severe cases of prostration following this procedure and attributable to faulty technic, acacia is considered by many the best agent for this purpose. In some clinics the injection is employed as a regular routine to prevent shock and in treating such conditions as eclampsia and edema. At least a partial explanation of its action is in delaying elimination of the salt.

Tragacanth is used for the manufacture of pills, emulsions, troches, and pastilles but is not generally regarded so highly as acacia. It is, however, much less easily fermented than the latter, and this is sometimes an important advantage.

3. Starch and Dextrin

Starch (Amylum), U.S.P., B.P. The granules separated from the grain of *Zea Mays* (*Gramineæ*).

Glycerite of Starch, U.S.P., B.P.

Starch paste is a good demulcent base or vehicle for the administration of other remedies. The glycerite is an emollient preparation for application to chapped hands, sunburn, etc. Any demulcent may be added to enemas to prevent irritation and increased peristalsis, but starch is usually preferred. It is presumed to be an antidote for iodine poisoning by forming blue starch iodide. The nutrient value of starch, which needs no discussion here, is utilized in medicine to a great extent in the feeding of convalescents and invalids. The reputed advantage of **arrowroot, tapioca**, and **sago** has not received scientific proof, although the flavor may be more agreeable than that of starch from other cereals. Starch is also employed as a dusting powder for the skin and to keep pills and tablets from adhering. Barley water is a common adjunct for administering large quantities of fluid to assuage thirst in fever and to dilute milk for infant's food. Dextrin forms the chief substance of ordinary mucilage and can be used as demulcent like acacia or starch.

4. Almond

Expressed Oil of Almond (Oil of Sweet Almond), U.S.P., B.P. The fixed oil obtained from the kernels of varieties of *Amygdalus communis* (*Rosaceæ*).

Although sweet almond contains the ferment, emulsin, amygdalin is not a component, so that a bland emulsion is formed when it is triturated with water. This can be used in the pharynx, bronchi, stomach, or intestine as a demulcent. The fixed oil is an emollient like other fats, but its cost is a great drawback to extensive employment. For elegant hand lotions and ointments the flavor is very popular. The nutrient value is highly esteemed, especially in the form of almond bread for diabetics, since it contains comparatively little starch but plenty of fat and some protein.

5. Triticum

Triticum (Couch or Dog Grass, Agropyrum), N.F. The dried rhizome and roots of *Agropyron repens* (*Gramineæ*), Dose: 10 Gm., 2½ drachms.

Fluidextract of Triticum, N.F. Dose: 10 cc., 2½ fluidrachms.

Couch grass formerly enjoyed considerable undeserved reputation as a remedy for infections of the urinary tract and as a diuretic. The decoction is used by the laity as a drink in fever and for various diseases of the urinary canals. Any benefits derived are probably from the large amount of fluid, rendered more pleasant by the demulcent drug.

6. Althea

Althea (Marsh Mallow Root), U.S.P. The dried root of *Althæa officinalis* (*Malvaceæ*), deprived of the brown, corky layer and small roots.

Syrup of Althea, N.F.

Marsh mallow and common mallow are used by the laity as demulcent infusions or decoctions for various affections of the mouth and throat, but in medicine they are employed much less than formerly. Althea is frequently used as an excipient for pills.

7. Gelatin and Chondrus

Gelatin, U.S.P., B.P. A product obtained from animal tissues, such as skin, ligaments, and bones.

Glycerinated Gelatin, U.S.P.

Gelatin Compound Phenolized, N.R.

Chondrus (Irish Moss, Carrageen), N.F. The dried, bleached plant of *C. crispus* or of *Gigartina mamillosa* (*Gigartinaceæ*).

Mucilage of Chondrus, N.F.

In pharmaceutical manufacturing, gelatin capsules and coatings are sufficiently familiar. The jelly has been deemed an excellent food for invalids, since it can replace about half of the protein diet; and, furthermore, since no indol is formed from it, it is considered valuable in intestinal putrefaction. Some nutritional authorities, on the contrary, affirm that gelatin is useless to secure growth and can be only an emergency food. It has some use as a demulcent vehicle for other medicaments, such as in suppositories. The compound phenolized solution was introduced for the local treatment of ulcers and unhealed secondary burns.

Subcutaneously and *intravenously*, gelatin has been administered to prevent bleeding by increasing the coagulability of the blood. Opinions are pretty well divided as to the clinical efficacy, the majority probably being favorable. The temperature is raised greatly, and the injection is quite painful; there is also danger of tetanus infection. Some have claimed that oral administration is equally effective, recommending several ounces per day. Gelatin has also been injected into the blood stream to prevent shock after hemorrhage by maintaining the blood volume.

Irish moss, which was formerly considered to be highly nutritive, is now known to be but slightly digested. Although it swells up with water like gelatin to form an insipid jelly which might be used as a demulcent, this has practically no advantage over other drugs of the class. Cetraria (Iceland Moss) is still highly prized in Scandinavian countries as an article of food, but its medicinal use as a demulcent and nutrient is practically obsolete in this country.

8. Elm

Elm (Ulmus, Slippery Elm Bark), N.F. The dried inner bark of *Ulmus fulva* (*Ulmaceæ*).

Troches of Elm, N.F.

The bark is much used in domestic medicine as a demulcent tea and, in the form of lozenges, for hoarseness and sore throat.

9. Oat

Oat (Avena), N.F. The grain of *Avena sativa* (*Gramineæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Oat, N.F. Dose: 4 cc., 1 fluidrachm.

This cereal, so widely consumed as a food, has been credited as a diuretic and laxative but is only rarely employed in medicine as a demulcent. Occasionally the meal is made into a poultice. Tincture of green oat has been prescribed by the homeopath.

Other Demulcents

Quince seed (*Cydonia vulgaris*), formerly official, is very commonly added to lotions, especially for the hands. Salep, similar to tragacanth, okra pods, mullein (verbascum) flowers and leaves, sassafras pith, coltsfoot, and ispaghula are sometimes employed as demulcents.

Of the substances used chiefly for other purposes, many are possessed of properties which might place them in this class.

Among these might be mentioned all of the sugars, the fatty substances usually applied externally as emollients, agar, malt, manna, fig, prune, castor oil, and cod liver oil. One of the best of these is glycerin.

EMOLLIENTS

Emollients are to the skin what the demulcents are to the mucous membranes. They are bland substances which *soften, relax, and protect the epidermis*, prevent the evaporation of water, and promote the absorption of other drugs through the skin. Most of them are animal and vegetable fats which easily become rancid and thus unfit for use, but petroleum products and wool fat are free from this disadvantage. The fats have very high nutritional value and can be used as foods.

The emollients are *employed* as a covering and protection to the skin for treatment or prevention of sunburn, chapped hands, abrasions, ulcerations, burns, the effects of irritating poisons, etc. They are quite generally used as vehicles for some other medicaments, but it is highly probable that they would be equally efficient alone, at least in many cases. One important application is in promoting absorption of drugs through the skin (inunction), either for deep penetration or even for systemic effect (mercury). They are effective as demulcents for the alimentary tract when administered by mouth or rectum, but the oily taste is objectionable to some. In addition, they lubricate the intestinal walls and stimulate peristalsis, and several of them are highly considered as foods.

1. Glycerin

Glycerin (Glycerol), U.S.P., B.P. $CH_2OH{\cdot}CHOH{\cdot}CH_2OH$. Dose: 4 cc., 1 fluidrachm, U.S.P.

Suppositories of Glycerin, U.S.P., B.P.

Applied to the unbroken skin, glycerin causes considerable smarting, on the abraded skin intense pain, because of its dehydrating action. In either case this soon ceases, and glycerin then behaves as a protective. It softens the epidermis and prevents cracking and roughness, for which purpose it is best diluted with two or three volumes of water (rose water). Applied in the rectum in doses of 5 to 8 grams, it acts as an efficient laxative if the doses are not repeated very often. Similarly it stimulates contractions when applied to the cervix uteri, the favorite form for such treatment being a suppository. In not too great dilution glycerin has distinct bactericidal character, a fact which explains its use as a food and drug preservative, also its topical application to wounds. Sclerosing injections of 50 to 75 per cent for varicose veins and hemorrhoids are sometimes recommended.

Internally glycerin is employed as a demulcent for coughs, sore throat, and hoarseness, as an adjuvant laxative, and as a vermicide for intestinal trichinæ or muscle-threadworms. As a nutrient to replace carbohydrate, one might note that its calorific value is about equal to that of the sugars and that, according to some reports, it can be used up to 100 grams daily without deleterious effects. Some derangement of digestion and laxative action are claimed by others.

In pharmacy glycerin is much employed as a solvent, as a vehicle, as a flavor, as an excipient, and as a preservative.

2. Petrolatum

Petrolatum (Soft Paraffin, Petroleum Jelly, Vaseline), U.S.P., B.P. A purified, semisolid mixture of hydrocarbons, obtained from petroleum.

White Petrolatum, U.S.P., B.P.

Liquid Petrolatum (Liquid Paraffin, Mineral Oil), U.S.P., B.P. A mixture of liquid hydrocarbons obtained from petroleum. Dose: 15 cc., 4 fluidrachms, U.S.P.

Liquid Petroxolin (Liquid Petrox), N.F.

Solid Petroxolin (Solid Petrox), N.F.

Petrobran, N.R.

The heavier products like vaseline are used as ointment bases and as vehicles for other drugs. In spite of chemical differences, they resemble the fatty emollients and present the advantages of indifference to reagents and of not deteriorating. They are not absorbed, have no food value, and cannot be used for inunction.

The oils are *used* as vehicles for sprays, for subcutaneous injection of other drugs, and for producing bowel movement, for the last purpose being given in doses of about an ounce just before retiring. Since the laxative action is not very strong, other purgatives are often mixed with the heavy oils. The mechanism of action is probably a combination of lubrication, inhibition of water retention, increasing bulk of the feces, and enhancement of peristalsis. Occasionally petrolatum causes nausea and quite frequently the oil leaks from the anus or is expelled by gas. In spite of these disadvantages, it is probably the least objectionable of substances to treat constipation. It was formerly claimed that use of this drug would tend to coat the intestinal walls to retard digestion and also that it removes fat-soluble vitamins from the food to prevent assimilation. However, most evidence collected during the past few years seems to refute both claims.

If the petroleum products are not purified properly, they may contain some of the lower boiling ingredients and thus cause *poisoning*. Kerosene on the skin is mildly irritating, strongly so on an abrasion, and it causes considerable gastro-enteritis in the alimentary tract. Gasoline and benzin are distinctly narcotic, giving rise to intoxication similar to that of alcohol, although the absorption is very slow. Instances of gasoline addicts have occurred from time to time. It brings about its effects much more readily when inhaled, the most important symptoms being headache, intoxication, and unconsciousness, with an asphyxial sequel. The treatment consists in fresh air, artificial respiration, and stimulants if necessary. Continuous handling of any petroleum products may give rise to this narcosis and may also lead to chronic skin eruptions and growths.

Crude oil and kerosene have been seen for years as anti-parasitics, especially against head-lice, and more recently for all diseases of the scalp, although they are unscientific and generally unsatisfactory. Deodorized kerosene was introduced for these purposes and is certainly, less disagreeable. It is also used as a convenient vehicle for other substances.

3. Vegetable Oils

Olive Oil, U.S.P., B.P. The fixed oil obtained from the ripe fruit of *Olea europaea* (*Oleaceæ*). Dose: 30 cc., 1 fluidounce, U.S.P.

Cottonseed Oil, U.S.P., B.P. The refined, fixed oil obtained from the seeds of cultivated varieties of *Gossypium herbaceum* or of other species of *Gossypium* (*Malvaceæ*).

Corn Oil, U.S.P. The refined, fixed oil from the germ of *Zea* (*Gramineæ*).

Sesame Oil (Teel Oil, Benne Oil), N.F., B.P. A fixed oil obtained from the seeds of one or more cultivated varieties of *Sesamum indicum* (*Pedaliaceæ*).

Arachis Oil (Peanut Oil, Earth-nut or Ground-nut Oil), B.P. The oil expressed from the seeds of *Arachis hypogaea.*

All of these oils are alike in properties, with but minor differences, and can be used therapeutically in the same way. Olive oil is generally regarded as having a superior flavor, but in this country corn and cottonseed oil, owing to cheapness, are often given preference. They are employed as external dressings for burns and abrasions and as vehicles for liniments. Introduced into the colon, they act as laxatives by softening the feces and lubricating the canal. The oils act as laxatives in a similar way when given orally, at the same time protecting the mucous membranes and relieving the pain caused by irritants. Olive oil will often apparently cure a biliary colic and is frequently recommended as a lithontriptic or stone remover, but if there is any such action, it cannot be any more than mere lubrication of the biliary duct. All of the oils are highly nutrient and can be used for this property by mouth, rectum, or inunction, as foods in malnutrition and wasting fevers. They are also injected into the thorax (oleo-thorax) for immobilization in the treatment of tuberculosis.

4. Theobroma

Theobroma Oil (Cacao or Cocoa Butter), U.S.P., B.P. The fat obtained from the roasted seed of *T. Cacao* (*Sterculiaceæ*).

Unlike most of the vegetable fats, theobroma is a solid which melts at body temperature, making it particularly valuable for an emollient vehicle in ointments and suppositories and as a lubricant in massage. Furthermore, it is not so reactive as other fats, which gives it importance as an excipient for pills of chemically active materials. It possesses high food value, being occasionally used for poor nutrition, especially in children.

5. Lard and Suet

Lard (Adeps, Prepared Lard), U.S.P., B.P. The purified internal fat of the abdomen of the hog, *Sus scrofa* var. *domesticus* (*Suidæ*).

Benzoinated Lard (Benzoated Lard), U.S.P., B.P.

Cerate (Simple Cerate), U.S.P.

Ointment (Simple Ointment), U.S.P., B.P.

Prepared Suet (Mutton Suet), U.S.P., B.P. The internal fat of the abdomen of the sheep *Ovis aries* (*Bovidæ*), purified by melting and straining.

Lard is employed as a soft ointment base for emollient medication. It has the disadvantage of disagreeable odor and ease of deterioration, both of which are obviated by adding a small quantity of benzoin to act as a preservative and conceal the odor. Being easily decomposed, as is lard, suet may be preserved by benzoin in the same way. It is harder than lard at room temperature and produces stiffer ointments.

6. Linseed

Linseed (Linum, Flaxseed), U.S.P., B.P. The dried ripe seed of *Linum usitatissimum* (*Linaceæ*).

Crushed Linseed, B.P.

Linseed Oil (Raw Linseed Oil), U.S.P., B.P.

Linseed contains a mucilaginous material and much fat, so that it is both demulcent and emollient. Decoctions of the drug have for years been regarded by the laity as an efficient remedy in bronchitis and diseases of the mucous membranes in general. The crushed seed is mixed with water to make a poultice much used as a counter-irritant and "drawer." The expressed oil has a disagreeable odor and is employed very little except in veterinary practice and in a few liniments. The boiled oil is of no value in medicine and should not be dispensed. The reaction of linseed oil and sulphur furnishes the famous Harlem oil. The seed is somewhat laxative and is frequently added to wheat for breakfast foods in the treatment of chronic constipation.

7. Stearic and Oleic Acids

Stearic Acid, U.S.P. Chiefly $C_{17}H_{35}\cdot COOH$.

Oleic Acid, U.S.P., B.P. Chiefly $C_{17}H_{33}\cdot COOH$.

Stearic acid is a hard, glossy solid used occasionally alone as an emollient in skin diseases but usually with carbonates in the manufacture of suppositories. Oleic acid is somewhat irritating and, for that reason, is never used alone, being limited to the preparation of ointments of basic materials, the oleates.

8. Wax and Spermaceti

Yellow Wax (Beeswax, Cera Flava), U.S.P., B.P. The purified honeycomb of the bee, *Apis mellifera* (*Apidæ*).

White Wax (Bleached Beeswax, Cera Alba), U.S.P., B.P.

Spermaceti (Cetaceum), U.S.P. A waxy substance obtained from the head of the sperm whale, *Physeter macrocephalus* (*Physeteridæ*).

Beeswax melts at about 65°C. and is quite stable to reagents, so that it is much used to stiffen emollient ointments, cerates, and plasters. Spermaceti is employed in the same manner, mainly for elegance in pharmacy. Occasionally it is found as an ingredient of dusting powders for the feet.

9. Wool Fat

Wool Fat (Suint, Adeps Lanæ), U.S.P., B.P. The purified, anhydrous, fat-like substance from the wool of sheep, *Ovis aries* (*Bovidæ*).

Hydrous Wool Fat (Lanolin), U.S.P., B.P.

Wool fat consists to a large extent of cholesterol, with smaller amounts of high-molecular paraffin alcohols and cholesterol esters of fatty acids. It was introduced into medicine in the belief that, since its composition is very near that of skin fat, it would be more readily absorbed than other oils, but this has not been demonstrated. Wool fat has the advantage that it does not easily become rancid, that it will emulsify other oils and fats, and, since it will readily absorb water, that it can be used to incorporate aqueous solutions for external application. The anhydrous form is quite sticky, and the hydrous form is hard, so it is usually used mixed with an oil or petrolatum. Wool fat is an efficient emollient for wrinkles, chapped hands, skin diseases, etc., and is used as an emulsifying vehicle for external preparations.

Cholesterol, which is a normal constituent of the body, is more or less an unknown quantity. In spite of very extensive studies to determine source and function, we have yet learned very little concerning these matters. There seems little doubt that cholesterol is synthesized in the body, probably in the sebaceous glands, and that it circulates in the blood and is ultimately utilized or destroyed. The amount is low in some diseases (infections) and high in others such as diabetes and nephrosis. It has been said that excessive amounts cause arteriosclerosis, since this condition appears to be caused in animals by administration of cholesterol. We also know that there is a close relation with the sex hormones and with some of the vitamins.

Cholesterol has been used locally in the treatment of common alopecia but is probably as little effective as other agents of this class. It has also been administered locally as a vulnerary and internally in asthma and in infections.

Other Emollients

Occasionally there will be calls for other animal and vegetable fats. Goose grease, cocoanut oil, and bear grease are often kept in stock, while dog grease and butter are sometimes used in domestic therapy. These have no advantages in any respect, regardless of the extravagant virtues which some ascribe to them.

Among the substances used mainly for other purposes, there should be mentioned a few which are typically emollient and often applied in that way. Castor oil and cod liver oil are the most important of these, but we might also include ichthyol, many of the demulcents, chaulmoogra oil, and soap.

DETERGENTS AND EMULSIFIERS

Emulsifying agents are viscid, usually gummy materials, which are used to break up insoluble powders or oils and fats, to envelop the particles so formed, and to keep them apart so that a suspension is made. The most common agents for this purpose are the mucilaginous demulcents, especially acacia and tragacanth, but egg yolk, soap bark, malt extract, bile salts, ethanolamine, soap, etc., may be useful. The alkalies are effective, but in this instance the irritation resulting is of great disadvantage in making medicinal emulsions.

The emulsifying substances are used to suspend insoluble powders and oils in order to allow dilution and admixture and to facilitate absorption. Any of them will clean (deterge), this action being due to the mechanical effect from foam, to the isolation of grease, and to softening of the epidermis.

1. Soap

Soap (Olive Oil Castile Soap, Hard Soap, Sapo Durus), U.S.P., B.P. Soap prepared from olive oil and sodium hydroxide.

Camphor and Soap Liniment (Liquid Opodeldoc), U.S.P.

Soft Soap (Sapo Mollis, Sapo Viridis, Sapo Kalinum, Green Soap), U.S.P., B.P. Soap made with linseed oil.

Liniment of Soft Soap (Tincture of Green Soap), U.S.P., B.P.

Curd Soap (Sapo Animalis), B.P.

Sodium Stearate, U.S.P.

Soap dissolves mucus, softens the skin and hair, and emulsifies fats. It is, therefore, used externally as a detergent and as a vehicle for liniments and inunction, serving the purpose of lubrication, emulsification, and cleaning. It is sufficiently caustic to cause rubefaction and quite frequently used in this way but is employed more often as a basis for other drugs in liniments and ointments and in tooth pastes and powders. Soap is an excellent vehicle for antiseptics, especially in skin diseases, as in compound cresol solution and in sulfur soap. Soap is itself fairly antiseptic, even in 2 to 3 per cent solution, as well illustrated in a large use in surgery for this purpose; energetic washing with sufficient soapy water is usually an adequate disinfection of the hands. In the form of suppositories or as an addition to enemas, it is irritating enough to render purgatives more efficient, giving a prompt and soft stool, but there seems to be considerable danger of injury to the membranes. The irritation of soap is also strong enough to promote growth of epithelium. In an emergency, soap can be an efficient antidote for corrosive acids, the alkali of hydrolysis being continuously and promptly neutralized by excess of acid. Concentrated soap solution is also fairly reliable as an emetic.

2. Quillaja and the Saponins

Quillaja (Soap Bark, Panama Bark, Soap Tree Bark), N.F., B.P. The dried inner bark of *Q. Saponaria* (*Rosaceæ*).

Tincture of Quillaja, N.F., B.P.

A number of closely related, non-nitrogenous glucosides of widely different origin are grouped together under the name of saponins. They are not crystallizable, are soluble in water or dilute alcohol, but are not dialyzable. Vegetable ferments are generally not effective, but acids hydrolyze them readily to sugars and sapogenins. They are either acid or neutral and are precipitated from solution by certain neutral salts such as ammonium sulphate. Shaken with water, the saponins produce a large quantity of persistent foam, because of an extensive lowering of surface tension, and, for the same reason, they will emulsify fats and insoluble powders. Even very dilute solutions (1:10,000) will produce a distinct lather.

Saponins are *found in* over 400 species of *plants* belonging to at least 50 families. In addition to quillaja, the most important are sarsaparilla, caulophyllum, senega, guaiac, and dioscorea. A number of others contain saponins as minor components, such as digitonin of digitalis and adonic acid of adonis. The venom of poisonous snakes resembles the saponins in properties, and the potent principles probably belong to this group.

All of the members have a harsh, acrid, or bitter taste, which excites a flow of saliva, and are markedly *irritating* to mucous membranes because of general protoplasmic poisoning. Applied to the conjunctiva, there is a flow of tears with much pain and inflammation, and in the nasal passages sneezing and catarrhal symptoms. If taken into the gastro-intestinal tract, they provoke nausea, vomiting, and diarrhea, which may be accompanied by blood and considerable colic. Applied to the skin for a short time, there is little effect, but long-continued action may give inflammation and systemic poisoning from slow absorption. Most of the saponins are absorbed very little from the skin or mucous membranes but readily from abraded surfaces. That from agrostemma (corn cockle) is, however, different from the rest in that it is promptly taken up from the intestinal canal to give dangerous symptoms. Subcutaneous injections give rise to local inflammation and continuous systemic toxicity, such as is observed quickly and severely after intravenous administration. The symptoms are convulsions and subsequent paralysis, death occurring by respiratory failure. When the dose is not too large, the alimentary effects may be presented, often also depression, loss of appetite, diuresis, irregularities in the pulse and respiration, nausea, vomiting, and purging. All of the saponins will lake blood readily, but this is not the cause of effects upon the nervous system, for cholesterol will prevent the hemolysis without affecting the course of poisoning. One of the saponins of sarsaparilla will lake blood in a concentration of 1:400,000 and will completely dissolve the corpuscles 1:125,000.

The saponins are probably useless *in medicine* except perhaps as nauseant expectorants and emetics. They are good cleansing agents and emulsifiers but must be considered too dangerous for extended employment. Quillaja is often used in the arts for cleaning where alkalies or soap might be detrimental. The exceedingly high toxicity to fish can be utilized for the purpose of killing them, but the extent of this is limited. The tendency to employ various saponin-containing drugs for the production of foam on soft drinks should be severely condemned; some of them may be safe, but they all require more study.

3. Egg

Egg (Ovum Gallinaceum), N.F. The recently laid egg of the hen, *Gallus domesticus* (*Phasianidæ*).

Fresh Egg Yolk, N.F.

Glycerite of Egg Yolk, N.F.

Both parts of the egg are efficient emulsifiers for insoluble substances, the yolk being more so and usually preferred. They are used chiefly in the preparation of liniments, also as nutrients, and for the lecithin content.

4. Ethanolamine

Triethanolamine, N.R. A mixture of $(C_2H_4OH)_3N$ with about 25 per cent of the mono and di derivatives.

This excellent emulsifying agent is used in various ointments and in other preparations for use on the skin and scalp. It combines with fatty acids to form soaps which are good cleansers and can be incorporated with aqueous or oily media.

DENTIFRICES

Dentifrice (Tooth Powder), N.F.

Chalk and orris are the usual *bases* for powders; soap for pastes. To these are generally added flavoring agents and some substance designed to give an antiseptic action or to confer on the preparation a favorable action on the gums. The materials which are presumed to accomplish the latter purpose are potassium chlorate, myrrh, pyrethrum, and the volatile oils. Of the numerous antiseptics encountered, salicylic acid, thymol, peroxides, sodium perborate, benzoates, and menthol are common.

Emetine has been added, on the basis that it is inimical to the micro-organism which is presumed to cause pyorrhea.

It is now known that any attempts to kill all bacterial life in the oral cavity by drugs must end in failure. For this reason most manufacturers of tooth preparations and mouth washes are today laying more stress on the *cleansing* character only, which is the real value of such articles. Strongly to be condemned are the extravagant claims by some advertisers that certain tooth pastes can make teeth white, cure halitosis, prevent pyorrhea, or correct other abnormalities.

ALIMENTARY AND DUSTING POWDERS

Inert powders may serve a very useful purpose in therapeutics when they are applied to the skin or to mucous membranes. They cover and protect the part, prevent friction or irritation, and, by absorbing liquids, dry the tissues, forming an impenetrable crust which prevents the growth of bacteria. While the action is local and purely mechanical, the effect may be far-reaching and is strictly therapeutical. The efficiency externally will depend somewhat upon occlusive power but not entirely, since melting point, specific gravity, fineness, and other properties also play a part. The absorptive capacity varies not only with the different powders but also with the nature of the substance to be occluded. Kaolin or starch takes up about 75 per cent of water, while talcum will absorb only about 60 per cent, and, on the other hand, animal charcoal, which occludes some water, will absorb certain toxins and metallic poisons, while kaolin is ineffective. Internally, the same powders can serve an identical purpose in protecting the mucous membranes, but some of them (bismuth) may at the same time exert a minimum astringent and antiseptic action and hence receive preference for mucosa.

1. Charcoal

Activated Charcoal (Wood Charcoal, Carbo Ligni), U.S.P. The residue from the destructive distillation of various organic materials, treated to increase its absorptive power. Dose: 1 Gm., 15 grains.

Purified Animal Charcoal, N.F. Dose: 0.3 Gm., 5 grains.

Charcoal is *employed* to absorb toxins, colors, gases, etc., in infective intestinal diseases, alkaloidal poisoning, flatulence, and colic. Considerable debate has been waged as to its efficacy, since wet charcoal can have no great absorptive power. Nevertheless, because clinical opinion seems pretty well divided, no real decision can yet be drawn; much of the benefit may be attributed to a mechanical protection, but it is difficult to imagine all reported results due to this alone. The remarkable ability of dry charcoal to occlude oxygen in an active form has led many to say that it thus acts as an indirect oxidizing agent, establishing aerobic conditions which are fatal to pathogenic organisms. Charcoal was much used formerly in the form of poultices for external application to wounds, but modern development has substituted cleaner and surer means of wound treatment. Animal charcoal, especially if freed from mineral matter, is more absorptive than that from wood and contains smaller and less irritating particles, and it is claimed to be much more effective in all cases. Any form may be used to determine the time interval of food in the intestinal tract, because the feces are colored black.

In recent years carbon has been injected intravenously and in other ways for several diseases and particularly for pulmonary tuberculosis. This apparently unreasonable procedure has received considerable support from many who have tried it, but an increasing number of controlled experiments have been reported which argue for its ineffectiveness. Several deaths may have been caused by the injection.

2. Lycopodium

Lycopodium, U.S.P. The spores of *Lycopodium clavatum* (*Lycopodiaceæ*).

This is a light-yellow, mobile powder which has a remarkable power for absorbing liquids, but which is otherwise inert. It is used in pharmacy mainly for this property and also sometimes as a dusting powder for infants. It was formerly considered to be diuretic but is no longer administered internally.

3. Talc and Siliceous Earth

Purified Talc (*Talcum Purificatum*), U.S.P. A purified, native, hydrous magnesium silicate, sometimes containing a small amount of aluminum silicate.

Purified Siliceous Earth (Purified Kieselguhr, Purified Infusorial Earth, Terra Silicea Purificata), U.S.P. A form of silica consisting of the frustules and fragments of diatoms, purified by boiling with diluted hydrochloric acid, washing, and calcining.

These inert powders are employed largely as dusting powders, as filtering agents in the preparation of aromatic waters, and also sometimes as an internal protection to the intestinal mucous membrane.

4. Kaolin

Kaolin (*Bolus Alba,* White Clay), N.F., B.P. A native hydrated aluminum silicate, powdered, and freed from gritty particles by elutriation.

Cataplasm of Kaolin (Poultice of Kaolin), N.F., B.P.

White clay is used as a dusting powder to irritated spots or abrasions of the skin. It is said that repeated applications to the nose and throat will sterilize these areas within a short time. Occasionally it is employed internally to check diarrhea, the high occlusive power of kaolin probably playing the most important role. The clay poultice has attained considerable popularity as a counter-irritant under the proprietary name of antiphlogistine, which owes any success that it may have to heat retention. It has been shown that flaxseed is much better for this purpose. The adsorption by kaolin may also be used for clarification of colored materials and for removal of toxic substances, such as alkaloids and toxins, but the value of the method is not high.

5. Pumice

Pumice, N.F. A substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium, and sodium.

Pumice is mainly of laboratory value in making solutions of difficultly soluble materials and as an absorbent.

6. Cerium Oxalate

Cerium Oxalate, N.F. A mixture of the oxalates of cerium, didymium, lanthanum, etc. Dose: 0.2 Gm., 3 grains.

This mixture has properties similar to the insoluble bismuth compounds and is very commonly used as a substitute for these in the gastro-intestinal tract, chiefly in obstinate cases of vomiting. It has, however, little if any advantage. Cerium ammonium nitrate is claimed to be efficient as a remedy in tuberculosis, as is also the rare element, samarium.

Other Powders

Another powder often applied in the same way as talc and kaolin is finely divided **tripoli,** also a commercial addition to cleaning and polishing preparations.

Those drugs, whose chief use is in other lines but which are often given preference as dusting powders, are starch, boric acid, calcium carbonate, zinc oxide and stearate, calamine, and magnesia. Iodoform, salol, lactose, wax, spermaceti, lime, acetanilid, salicylic acid, and the insoluble local anesthetics are also employed.

PLASTERS, POULTICES, AND BANDAGES

These afford protection against mechanical irritation and infection in the same way as do dusting powders. The poultices and plasters may sometimes be used to secure counter-irritation.

1. Cotton Products

Purified Cotton (Absorbent Cotton), U.S.P. The hairs of the seed of cultivated varieties of *Gossypium herbaceum*, or of other species of *Gossypium* (*Malvaceæ*), freed from adhering impurities and linters, and deprived of fatty matter.

Pyroxylin (Soluble Gun Cotton), U.S.P., B.P. A product obtained by the action of a mixture of nitric and sulfuric acids on cotton, and consisting chiefly of cellulose tetranitrate, $C_{12}H_{16}O_6(NO_3)_4$.

Collodion, U.S.P.

Flexible Collodion, U.S.P., B.P.

The common applications of cotton in the form of lint, gauze, and bandages need no special discussion. Collodion is employed to protect small wounds ("new skin") and as a vehicle for the application of other drugs. The quick evaporation of the alcohol and ether leaves a thin, firm film which mechanically covers the part. This film is easily cracked and torn, a disadvantage which is offset by adding oil, as in flexible collodion.

Cellulose acetate, which is now so extensively used for the production of rayon, package wrappers, etc., makes an efficient substitute for pyroxylin in preparing collodion. It is also said to be better than paraffin for correcting deformities.

2. Paraffin

Paraffin (Hard Paraffin), U.S.P., B.P. A purified mixture of solid hydrocarbons, obtained from petroleum.

Paraffin Ointment, B.P.

Paraffin Dressing (*Curatio Paraffini*), N.F.

Parresine, N.R.

Paraffin is extensively used as a protective covering for wounds and, especially, burns. For this purpose, it should be pliable and yet strong at body temperature, attributes not possessed by the official product. It is also employed to prepare impregnated bandages and to seal dressings. The inert character of paraffin makes it of some value in the correction of deformities, especially of the nose, by injecting it under the skin. Although there is presumed to be some danger of interfering with circulation, and although the results may often be impermanent, skilled surgeons have reported satisfactory results over more than thirty years.

3. Adhesive Plaster

Adhesive Plaster (Elastic or Rubber Plaster), U.S.P., B.P. A mixture of rubber, resins, and waxes, with a filler of an absorbent powder, such as zinc oxide, orris root, or starch, mechanically mixed and spread upon cotton cloth.

4. Mastic

Mastic, N.F. A concrete resinous exudation from *Pistacia Lentiscus* (*Anacardiaceæ*).

Mastic was formerly thought to possess medicinal virtues similar to those of turpentine oil but is probably never prescribed at present. The chief applications are as dressing for wounds to prevent infection of surrounding parts and as a varnish for various purposes.

Other Plasters and Poultices

Similar to mastic and collodion are **court plaster, gutta percha,** and **sodium silicate,** all of which are familiar. **Plaster of Paris** is applied as a rigid dressing and for the manufacture of casts. Bread and flour are often made into poultices. Among the materials more useful in other ways, attention may be called to linseed, kaolin, oat, starch, and charcoal, which are not uncommon in the making of plasters and poultices.

ACTING LOCALLY—IRRITANT

Almost any foreign substance is more or less irritant to the skin and particularly to mucous membranes, because of the great reactivity of proteins. Even water will cause sufficient reaction to be useful therapeutically, if employed under suitable conditions. The effects are accomplished by coagulation, precipitation, or hydrolysis of the protoplasmic compounds, causing destruction of a few or a large number of cells. The ultimate result depends upon the nature of the irritant, its volatility, concentration, and chemical properties, upon the duration of exposure, upon sensitiveness of the part, upon rapidity of penetration, and upon other factors.

The first result is usually a congestion and redness, due to reflex action upon the peripheral nerves, with itching and burning, or even considerable pain. The area becomes larger, with possible loss of sensation, but if the drug is removed at this stage, the tissues gradually return to normal, although the pain may persist for a long time, and the upper layers of cells generally slough. An agent used for the purpose of reddening only is called a *rubefacient,* and the process *rubefaction.*

If the drug is left on for further action, serum begins to exude through the lower layer of skin and appears in small globules under the epidermis which it cannot penetrate. Coalescence of these globules gives a large blister between the skin layers. The exudate is at first clear but later becomes cloudy with leucocytes. If the action is halted at this point, healing takes place more or less readily without scar formation, although the place of application is usually apparent for a long time by a difference in pigmentation. The substances used to bring about the action are called *vesicants*, *blisterers*, or *epispastics*, and the process *vesication.* If the drug is unable to penetrate the epidermis, vesication occurs only at the gland orifices in the shape of small pustules, which may finally flow together. Continued action causes the inflammation to penetrate deeply, with the formation of a slowly healing abscess. Drugs of this nature are called *pustulants.*

Strong acids and alkalies, various metallic salts, and many other compounds may bring about destruction of tissues without blister formation. The preliminary action, however, presents all of the effects of inflammation, as does that from the rubefacients. The upper necrosed cells form a scab or scar, and the substances when used to destroy tissue are called *escharotics.*

The effects on mucous or serous membranes are similar, but since all layers are generally penetrable, no blistering can result except on intermediate surfaces like the mouth. Application in dilute form stimulates the under cells to reproduction and, in contact with gland tissues, increases secretions. On an abrasion, this stimulation may bring about rapid healing, although the superficial layers of cells are destroyed. Under such conditions the drug is called a *local stimulant.* Some substances which precipitate or coagulate the albumin of protoplasm have the effect of contracting and hardening tissue. These are termed *astringents.*

Therapeutically then, irritant drugs are employed (1) to produce rubefaction and vesication, (2) to promote healing, (3) to cause astringency, and (4) to destroy abnormal tissue. We shall discuss first those substances used chiefly as local stimulants.

LOCAL STIMULANTS

As has been stated above, mild irritation in any way tends to stimulate cell production and tissue growth by a destructive action on the superficial layers and by increased circulation. Almost any irritant can be used in this way, but several have attained importance as healing agents.

1. Balsam of Peru

Peruvian Balsam (Balsam of Peru), U.S.P., B.P. Obtained from *Toluifera Pereiræ (Leguminosæ).*

Balsam of Peru is a mild antiseptic and irritant used as an application to wounds, indolent ulcers, burns, bedsores, and in skin diseases, to promote healing and allay inflammation. It is also more or less efficient against pediculi and scabies (the itch), destroying eggs of the latter in a very short time with applications of 5 grams three times a day. Internally the drug is harmless but may irritate the kidneys. It is occasionally employed as an antiseptic and stimulating expectorant in bronchitis and as an intestinal or urinary antiseptic. Employment locally and hypodermically in tuberculosis is probably valueless.

2. Potassium Chlorate

Potassium Chlorate (Chlorate of Potash), U.S.P., B.P. $KClO_3$. Caution should be exercised in mixing it with easily oxidizable materials.

Tablets of Potassium Chlorate, N.F.

Gargle of Potassium Chlorate with Iron (Golden Gargle), N.F.

This chemical was introduced into medicine with a view to utilizing its well-known power of oxidizing, under the erroneous impression that this would be exerted in the body and thus serve to kill bacteria. It has a cool, saline taste and is readily absorbed and excreted unchanged, mainly by the urine and saliva, without having any special action except diuresis and diarrhea, possibly nausea and vomiting from large doses. In very large amounts, and occasionally with minute quantities, however, serious poisoning can occur. In abnormal conditions of the mucous membranes of the mouth and throat, it appears to have a favorable influence, which has not been satisfactorily explained. As a gargle or wash, it is used in stomatitis, tonsilitis, relaxed sore throat, hoarseness, etc. The internal use in pyelitis, cystitis, and diphtheria and to prevent abortion is to be condemned as too dangerous; the common tablets are particularly deleterious because the laity is not acquainted with the poisonous nature of potassium chlorate.

Toxicity from internal employment of the drug, while not so common as formerly, is yet fairly frequent. Death in a child has been caused by less than a gram, although recovery in adults has been observed with as much as 40 grams, and an ounce has been ingested without apparent effect. When poisoning does occur, however, the mortality is about 70 per cent. The symptoms may be observed at once (acute) or delayed some time (subacute) but in general follow the same route. There are some gastro-intestinal effects, but the most important are attributable to the destructive action upon the red blood corpuscles. The latter are destroyed in or out of the body, the hemoglobin is converted into methemoglobin, and the cellular debris is coalesced into masses which may block the vessels, especially in the kidneys, liver, and spleen. The salt itself is unchanged, being theoretically able to change any quantity of blood. Children and diseased persons are much more susceptible than are normal adults.

The *symptoms* of poisoning are nausea; vomiting; pain in the stomach; bloody diarrhea; cyanosis and yellow skin and membranes; headache; giddiness; anuria; bloody urine; muscular weakness; delirium; difficulty in breathing; rapid feeble pulse; asphyxia; coma; death. The organs are all found to be distended with blood, particularly the liver and kidneys, caused by cell debris blocking the vessels. *Treatment* is by gastric lavage, enemas, large quantities of hot drinks, and symptomatic. Transfusion or bleeding, with other measures to prevent shock, are said to be of benefit.

3. Calendula

Calendula (Marigold), N.F. The dried ligulate florets of *C. officinalis* (*Compositæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Calendula, N.F. Dose: 1 cc., 15 minims.

Tincture of Calendula, N.F. Dose: 4 cc., 1 fluidrachm.

Although extravagant claims have been made for marigold preparations as wound healers and for the treatment of ulcers and burns, most of this reputation is probably a remnant of folklore. Calendula is sometimes used like arnica as an application to sprains.

4. Coal Tar

Coal Tar (Pix Carbonis, Pix Lithanthracis), N.F., B.P. Obtained as a by-product in the destructive distillation of coal in the manufacture of illuminating gas.

Solution of Coal Tar (Liquor Carbonis Detergens), N.F., B.P.

Ointment of Coal Tar, N.F.

Coal tar is occasionally used as a healing ointment in skin diseases and on wounds, the antiseptic properties being of aid in preventing infection.

5. Scarlet Red

Scarlet Red (Biebrich Scarlet, Scarlet R.), N.F., N.R. Toluylazo toluylazo betanaphthol, $CH_3{\cdot}C_6H_4{\cdot}N_2{\cdot}C_6H_3(CH_3){\cdot}N_2{\cdot}C_{10}H_5OH$.

Scarlet Red Sulfonate, N.R. The sodium salt of azobenzene disulfonic acid azobetanaphthol, $C_6H_4(SO_3Na){\cdot}N_2{\cdot}C_6H_3(SO_3Na){\cdot}N_2{\cdot}C_{10}H_5OH$.

Dimazon, N.R. Diacetylaminoazotoluene, $CH_3{\cdot}C_6H_4{\cdot}N_2{\cdot}C_6H_3(CH_3){\cdot}N(COCH_3)_2$.

Biebrich scarlet has a remarkable power to stimulate the growth of epithelium and has been used for years in 2 to 10 per cent ointment to promote healing in burns, wounds, and ulcers. The higher concentrations may become decidedly irritating, and symptoms of aniline poisoning have been observed, so it is considered best to alternate it with a bland emollient. The other dyes, dimazon and scarlet red sulfonate, are employed in a similar way. The former, which is claimed to be non-staining, is used in 2 per cent oil solution or in the form of a 1:5 mixture with talc as a dusting powder.

6. Maggots

Surgical Maggots, N.R. Larvæ of *Phormia regina,* marketed on a medium of liver and agar.

The maggots are employed in the treatment of chronic osteomyelitis and other suppurative infections and sometimes of wounds in general. The mechanism of action is presumed to be removal of dead tissue, although other such agents do not accomplish this nearly so well. Great care must be exercised in preparation to insure freedom from deleterious microbes and presence of viable larvæ.

Extracts are said to be just as effective and to possess much advantage. On the other hand, others claim that the extracts are useless. Allantoin, which is found in them, is said to be an excellent healer, as is also urea, of which it is a derivative.

Other Local Stimulants

No list can be given here of all other drugs which have been used for the purpose of local stimulation, because they are almost numberless. Any substance which is irritating can be so applied; the stronger ones can be diluted. All alkalies and alkaline salts, most compounds of the heavy metals, many of the stronger antiseptics, volatile oils, balsams, escharotics, astringents, and counter-irritants have been converted to this purpose. It would be well to mention, however, a few substances which have attained much reputation as local stimulants. These are iodoform, silver salts, benzoin, myrrh, hydrastis, and coptis.

COUNTER-IRRITANTS

Counter-irritants, or **revulsants,** are drugs used to irritate the skin in order to modify or check affections in remote parts. The term *derivation* was formerly used to describe the process, on the basis that any effect is due to a drawing of blood from the distant area to the spot of application. The mode of action has been the subject of many theories, and it cannot be said to have been settled yet, but the more recent investigations indicate a complexity of operation. In part it is probably an alteration of the blood distribution, partly reflex effects through the nerve elements, and partly psychological. The method is one of antiquity and of considerably less importance now, not because it is ineffective, but because the limitations have been more definitely established. Clinical experience has certainly demonstrated the value of skin irritation as remedial in a variety of circumstances, for no matter what theories may be suggested and disproved, the essential facts obtained by experience show that pathological conditions can be, and are being, improved by counter-irritation. The extent of action depends upon the effect sought but is usually limited to rubefaction, occasionally extended to blistering.

The process is *used therapeutically* to reduce chronic inflammation in deep-seated organs, as in peritonitis, pleurisy, pericarditis, etc., or in parts adjacent, as in skin diseases and superficial infections. The inflammation is subdued, and any abnormal exudations are reabsorbed, the drugs used for the latter purpose being called *sorbefacients.* They are also employed to relieve pain of various kinds, either on the surface of the skin or in some internal organ or tissue. Thus, the discomfort of neuralgia, headache, sciatica, rheumatism, neuritis, and itching skin diseases is alleviated. Used over a large area, as in baths, the whole metabolism may be stimulated in an efficient manner, giving a sense of well-being, increased nutrition, and a general tonic effect. The irritation, since it brings more blood temporarily to the spot, will increase surface temperature and aid somewhat in the production of sweating. Finally, the irritation always has a reflex effect upon the central nervous system which may often be utilized to advantage in emergencies. The centers of circulation and respiration, as well as those which control the muscles, may be temporarily stimulated in case they are subnormal, as in collapse, fainting, anesthesia, narcotic poisoning, light coma, and asphyxia. The common use of smelling salts to bring about revival from fainting is a good illustration. In such cases the process is called *reflex stimulation.*

Summarizing, we may say that counter-irritants are employed to (1) subdue inflammation (derivative); (2) promote absorption of exudates (sorbefacient); (3) relieve pain (anodyne); (4) stimulate the metabolism (tonic); (5) promote sweating (diaphoretic); (6) stimulate the central nervous system (reflex stimulant).

1. Camphor

Camphor, U.S.P., B.P. A ketone, $C_9H_{16}CO$, obtained from *Cinnamomum camphora* (*Lauraceæ*); or produced synthetically (Synthetic Camphor). Dose: by mouth or hypodermic 0.2 Gm., 3 grains, U.S.P.; maximum 10 grains.

Camphor Water, U.S.P., B.P. Dose: 10 cc., 2½ fluidrachms, U.S.P.

Spirit of Camphor (Tincture of Camphor), U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.

Ampuls of Camphor, N.F. Dose: 1 cc. (about 0.2 Gm.).

Camphor Liniment (Camphorated Oil), U.S.P., B.P.

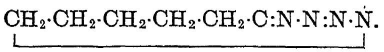
Ammoniated Liniment of Camphor (Compound Liniment of Camphor), B.P.

Solid Liniment of Soap (Camphorated Soap Liniment, Solid Opodeldoc), N.F.

Ointment of Camphor, N.F.

Monobromated Camphor, N.F. $C_{10}H_{15}OBr$. Dose: 0.125 Gm., 2 grains.

Metrazol (Cardiazol), N.R. Pentamethylenetetrazol,



$$\underbrace{CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot C{:}N\cdot N{:}N\cdot N}.$$

Dose: 0.1 Gm., 1½ grains parenterally, or orally 1½ to 4½ grains.

Camphor is a mild irritant and moderately antiseptic. On the skin it produces redness and inflammation; in the mouth, a burning taste and salivation, with a feeling of cold; in the nasal passages, a decrease in secretions. In moderate doses there is a sense of warmth in the stomach, but larger amounts produce symptoms of gastritis. It is also presumed to reduce secretions in the intestines and induce carminative action. Camphor is absorbed readily from all surfaces, although this is more or less erratic, and is excreted by the kidneys unchanged or in harmless combination with glycuronic acid, partly also by the lungs. After absorption there are a number of actions which are not well understood, probably because of variability in diffusion and in rapidity of elimination. All investigators are agreed that the normal circulation is practically unaffected, but the action on abnormal heart and vessels has been the subject of a great deal of discussion. In review, it seems that any stimulation must be decidedly inconstant and certainly of little importance in rational therapeutics. The respiration is affected little, if at all. In large doses camphor reduces abnormal temperature, probably by dilating the cutaneous vessels, and gives rise to delirium and convulsions of cerebral origin.

In medicine camphor is a useful counter-irritant, being applied in substance, in oil or alcoholic solution, or as an ingredient of poultices, plasters, or liniments. The mild antiseptic power adds some value in the case of septic inflammation. It is also a fair insecticide, especially for moths. Rubbed on the breast, it is presumed to reduce the secretion of milk, and it has been given orally and injected intramuscularly in doses of 1½ grains twice a day for the same purpose.

Camphor is administered *internally* as spirit or water to perform the role of antiseptic expectorant in bronchitis and of carminative in colic and flatulence. The irritant action is said to be useful against dyspepsia. The possible decrease in secretion of the intestines makes it an occasional remedy in diarrhea, particularly of infective character, where the antisepsis may play an important part.

The systemic actions of camphor, being unreliable and mostly very inconstant, are of considerably less importance. It has attained a great deal of popularity, given by hypodermic injection dissolved in olive oil, as an emergency *stimulant* to the circulation in cases of narcotic poisoning, febrile diseases, pneumonia, etc., but clinical opinions are about equally divided as to the benefits gained. The treatment is, however, apparently harmless. Camphor has been suggested as a specific in pneumonia, because of supposed susceptibility of the micro-organism, but the transient sojourn of the drug within the system would not appear to be effective. Like other irritants, camphor causes some reflex stimulation of the central nervous system, less than some others owing to the mildness of action, and has been recommended and used as an aphrodisiac. It has also been employed for years with the avowed attempt to stimulate the cerebral centers in order to stabilize the will power and motor mechanism. Thus it has been called a sedative in hysteria, chorea, epilepsy, and mania and, for the same reason, an anaphrodisiac. The advantages in any case are probably hypothetical. Large doses will reduce abnormal temperature, but there are more certain and safer means of accomplishing this object.

Large amounts induce the usual symptoms of gastro-enteritis with an additional transitory effect upon the central nervous system, causing excitation, sweating, diuresis, unconsciousness, and possibly convulsions. There is usually recovery, although death occasionally occurs. The treatment is as for any alimentary irritant, oils being avoided, since they increase the solubility and absorption.

Monobromated camphor is usually applied like other bromides as sedative and appears to have acquired a reputation for mild diseases of the respiratory passages, such as the common cold.

Metrazol is used like camphor as a stimulant, chiefly in cardiac insufficiency and in emergencies. Recently both metrazol and camphor have been injected to produce shock in the treatment of dementia praecox.

2. Turpentine

Turpentine (Terebinthina), N.F. A concrete oleoresin obtained from *Pinus palustris* and from other species of *Pinus* (*Pinaceæ*).

Oil of Turpentine (Spirits of Turpentine), U.S.P.

Rectified Oil of Turpentine, U.S.P., B.P. Dose: 0.3 cc., 5 minims, U.S.P.

Turpentine Liniment (Kentish Ointment), N.F., B.P.

Acetic Turpentine Liniment (White Liniment, Stoke's Liniment, St. John Long's Liniment), N.F., B.P.

Emulsion of Turpentine Oil, U.S.P. Dose: 2 cc., ½ fluidrachm.

Oil of Dwarf Pine Needles, U.S.P. The volatile oil distilled from the fresh leaves of *Pinus montana* (*Pinaceæ*).

Oil of Siberian Fir (*Oleum Abietis*, Pine Oil), B.P. The oil distilled from the fresh leaves of *Abies sibirica.*

Rosin (Resin, Colophony), U.S.P., B.P. The residue left after distilling the volatile oil from turpentine.

Rosin Cerate (Basilicon Ointment), U.S.P.

Compound Rosin Cerate (Deshler's Salve), N.F.

When oil of turpentine is *applied* to the skin, it gives reddening and burning and, after long application, vesication. It penetrates very readily and rapidly, and the blisters heal but slowly. On mucous membranes the irritation is much more severe, and, since absorption takes place quickly, the kidneys are stimulated somewhat, while secretions in the bronchi are decreased. It has no action in *small doses* except that due to irritation, being excreted finally by the kidneys and in smaller amounts by the skin and lungs. Large doses give rise to narcosis, delirium, and convulsions, with ultimate paralysis of the vital functions.

Turpentine oil is *used* as a counter-irritant in the form of poultices, liniments, stupes (cloth wrung out in hot water and then in the warm oil), or added to the bath in skin diseases and for general debility. In neuralgia it is said to be equally efficient by mouth. It should never be left on the skin longer than an hour unless well diluted. Like the other volatile oils, turpentine is employed in biliary colic and flatulence as a carminative, and by mouth or inhaled to decrease bronchial secretion and stimulate repair. It is at the same time definitely antiseptic and hemostatic, occasionally being applied locally on wounds or burns and on the site of operation. As an anthelmintic for tapeworms and threadworms and to produce diuresis, although fairly efficient, turpentine oil has been replaced largely by more agreeable drugs which have less irritation. It has, also, been used for an intestinal antiseptic in typhoid fever, the clinical evidence being very doubtful. Old oil was formerly presumed to be a reliable antidote for phosphorus because of peroxides formed on auto-oxidation, but the value is questionable, because unoxidized oil is an aid to the course of the poisoning. Frequently turpentine oil is added to purgative enemas to increase the efficiency. In addition, the administration of turpentine oil is claimed to be effective in subduing hysteria and hiccough and in dissolving gall-stones, both on unsupported grounds.

Rosin is mildly antiseptic and slightly irritant and sometimes applied to wounds and ulcers to promote healing. The principal value, however, is in the manufacture of stiff ointments and cerates.

The **pine-needle oils** are employed for many of the purposes to which turpentine is put, chiefly by spray or inhalation in respiratory infections and orally as antiseptic carminatives or diuretics, sometimes as counter-irritants in rheumatism. The more agreeable flavor of the needle oils may be considered an advantage.

3. Ammonia

Ammonia Water (Solution of Ammonia), U.S.P., B.P. An aqueous solution containing about 10 per cent of NH_3 by weight. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Stronger Ammonia Water (Strong Solution of Ammonia), U.S.P., B.P. About 28 per cent of NH_3 by weight.

Ammonia Liniment (Volatile or Hartshorn Liniment), N.F.

Ammonium Carbonate, U.S.P., B.P. Acid ammonium carbonate, NH_4HCO_3, and ammonium carbamate, $NH_4NH_2CO_2$, in varying proportions. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 10 grains.

Aromatic Spirit of Ammonia, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Anisated Spirit of Ammonia, N.F. Dose: 1 cc., 15 minims.

Ammonium Bicarbonate, B.P.

Ammonia is markedly rubefacient in strong solution and, if evaporation is prevented, vesicant. It penetrates the skin easily, giving rise to much pain and inflammation. On mucous membranes the irritation is very rapid and painful, bringing about an immediate and intense stimulation of the nervous system, which endures for but a short time. Inhalation of the vapor produces a quicker and deeper respiration after momentary standstill, increased pulse, and higher blood pressure. Concentrated solutions will cause rapid destruction of mucous membranes in the mouth, throat, and stomach, similar to that from the fixed alkalies. In addition, volatility diffuses the gas into the air passages, where the corrosive action may develop asphyxia. Whatever part is not changed in the stomach to ammonium salts is quickly converted by the liver into urea and rendered inactive. Injected subcutaneously, ammonia water has the same action as the ammonium salts except for the strong irritation previous to its neutralization. Ammonium carbonate is transformed, in the presence of water, to the hydroxide and, hence, acts as a solution of ammonia.

Any of the preparations may be *used* as counter-irritants, usually in the form of liniments but occasionally as blistering agents to replace cantharides, although the latter treatment is quite painful. They may be inhaled as emergency stimulants in cases of poisoning by narcotics, in fainting, or in collapse, generally being given as ordinary smelling salts. Too high concentration must be avoided, because large amounts may cause bronchitis or pneumonia from the severe irritation. Administered by mouth, ammonia behaves as an irritant, antacid, and carminative, while large doses are emetic. The aromatic spirit is a popular diffusible stimulant and is used in this way in digestive disturbances, sick headache, and after a debauch. The carbonate is added to cough mixtures to render the bronchial secretion more fluid. Ammonia water is applied locally for snake bites, where it can do little good, and for insect bites, where it may neutralize acid poisons.

4. Cantharides

Cantharides (Spanish Fly, Russian Fly), U.S.P. The dried insects, *Cantharis vesicatoria* (*Meloideæ*), yielding about 0.6 per cent of cantharidin.

Cantharidin, N.R., B.P. The inner anhydride, $C_{10}H_{12}O_4$, of cantharidic acid obtained from cantharides. Dose: 1/240 to 1/120 grain, N.R.; maximum 1/120 grain.

Tincture of Cantharides, U.S.P. Dose: 0.1 cc., 1½ minims, U.S.P.; maximum 10 minims.

Cantharides Cerate (Blistering Cerate), U.S.P.

Cantharides Plaster, U.S.P.

Cantharidin Plaster, B.P.

Blistering Liquid (Liquor Epispasticus), B.P.

Cantharidin is an active irritant when applied to the skin, but the effects are slow in developing, and the amount of pain is not great. Since it does not penetrate readily to the deeper layers, the blister formed is found to heal rapidly with a minimum of scar formation. On mucous membranes or on abrasions the action is much more severe, local tissue destruction leading to slow-healing and painful abscesses. Cantharidin is absorbed easily from any surface, although the amount taken in from the intact skin is small; it is excreted mainly in the urine, also by the intestines, for subcutaneous injection gives some enteric inflammation.

Cantharides is *employed externally* as a counter-irritant in the form of plaster for pleurisy, neuralgia, rheumatism, and other similar conditions. The irritation is carried to the stage of blistering, which requires 6 to 10 hours with the official plaster; the liquid is drained by lancing; and a dressing of oil is applied. As a blistering agent cantharides is probably supreme, but there is always more or less danger of poisoning. The tincture, largely diluted, has been prescribed as a local stimulant to treat baldness, but there is no reason to suppose its action different from that of any other irritant, and much of its efficiency, if any, may be psychological.

The drug has no specific action *internally* except local irritation, principally affecting the alimentary tract and kidneys and produced after any method of administration. The inflammation of urethra and bladder produces considerable pain, reflexly stimulates the sexual organs, and increases the quantity of urine. This would indicate the use of cantharides as diuretic, aphrodisiac, and emmenagogue, and it has frequently been so employed. The popularity for these purposes has waned, however, after numerous poisonings; in reality there has never been enough effect to justify the administration, except for diuresis, which can be accomplished more safely in other ways.

The *toxic effects,* which may arise after any mode of application, are all attributable to its very great power of irritation, especially on the kidneys and alimentary tract. The symptoms are burning sensation in the mouth and throat, thirst but inability to swallow, nausea, vomiting, possibly diarrhea, kidney pain, frequent urination, together with casts and albumin in the sediment, rapid pulse then slow and weak, fainting, difficulty in breathing, and collapse. If recovery takes place, it is long delayed. Poisoning has resulted from as little as 10 grains, and death by three times as much, but recovery has taken place after much larger doses. The treatment consists in washing out the stomach and in administering large quantities of aqueous liquids, never oils.

Cantharidin, which has taken the place of the crude drug in some pharmacopœias, is capable of more uniform dosage and is much more convenient and cleanly.

5. Mustard

Black Mustard (*Sinapis Nigra,* Brown Mustard), U.S.P. The dried ripe seed of *Brassica nigra* and *B. juncea* and varieties related to these species (*Cruciferæ*). Dose: emetic 10 Gm., 2½ drachms.

Mustard Plaster (Mustard Paper), U.S.P.

Volatile Oil of Mustard, U.S.P. A volatile oil obtained from black mustard or prepared synthetically. Dose: 0.008 cc., ⅛ minim, U.S.P.; maximum ½ minim.

Ointment of Mustard, N.F.

The official mustard contains a glucoside sinigrin and an enzyme myrosin, which at temperatures below 50°C. is able to hydrolyze the former to glucose, potassium bisulfate, and volatile oil of mustard, or allyl isothiocyanate. The oil is the only active constituent and is not formed until after the addition of warm water. White mustard, formerly official, contains a glucoside hydrolyzing to a fixed oil which is also irritant but less so than that from the black variety.

When *applied to the skin,* wet mustard causes considerable irritation which induces almost intolerable pain and, after sufficient time, blistering. The blisters are said to heal less rapidly than those from cantharides, because of deeper penetration and consequent greater volume of inflammation. Volatile oil of mustard is the most rapidly acting of all volatile oils and probably of all skin irritants. Applied to the skin, it produces almost instant vesication.

Therapeutically, the irritation is used only to the rubefacient stage whenever a counter-irritant is indicated. The official plaster is most commonly employed, left on for 15 to 30 minutes or until a sensation of tingling is experienced. Mustard may also be added to a linseed poultice (10 per cent), to a bath of warm water (about 10 grams per gallon), or to a foot bath. Reflex stimulation may be induced in this way, or the stimulation of surface circulation may serve the purpose of a diaphoretic. Delayed menstruation may sometimes be hastened by a warm mustard foot bath. In the mouth the drug is capable of exerting a powerful sialagogue action and infrequently is used in this way. A tablespoonful of mustard in warm water is often a useful emetic in cases of emergency, although it is considered very uncertain. The general employment of mustard as a condiment is occasionally applied in medicine to increase appetite and assist in digestion. It is said that inhalation of the volatile oil will relieve an earache.

6. Arnica

Arnica, N.F. The dried flower-head of *A. montana* (*Compositæ*). Dose: 0.2 Gm., 3 grains.

Tincture of Arnica, N.F. Dose: 1 cc., 15 minims.

Fluidextract of Arnica, N.F. Dose: 0.1 cc., 1½ minims.

Arnica contains a volatile oil which is described variously as stomachic, carminative, or stimulant. It has been used in alcoholic solution as a counter-irritant and internally in a variety of unrelated complaints. Its popularity with the laity as an external application for sprains and bruises has waned remarkably, and although it might theoretically be a reflex stimulant and carminative, it is usually considered too unreliable for any therapeutic purposes and too dangerous internally under any circumstances.

7. Formic Acid

Formic Acid, N.F. An aqueous solution containing 24 to 26 per cent of HCOOH. Dose: 0.3 cc., 5 minims.

Spirit of Formic Acid (Spirit of Ants), N.F. Dose: 4 cc., 1 fluidrachm.

Formic acid and its salts are claimed to be powerful stimulants to muscular action and kidney function, similar to caffeine and the other xanthine derivatives. They are occasionally used to retard fatigue and to promote diuresis, also in various other ways like diluted acetic acid and the acetates. The acid is applied or injected for counter-irritation under some circumstances and in the treatment of lupus and cancer.

8. Mezereum

Mezereum (Mezereon), N.F. The dried bark of *Daphne Mezereum*, *D. Gnidium*, or of *D. Laureola* (*Thymelaceæ*). Dose: 0.6 Gm., 10 grains.

The moistened bark will redden the skin and raise a blister, as does mustard, owing to the properties of mezerein, an acid anhydride, and of a glucoside daphnin. It is occasionally used as an ingredient of liniments or plasters, and the natives chew it as a sialagogue. It was formerly added to the so-called alterative mixtures, such as compound fluidextract of sarsaparilla.

Other Counter-irritants

Other drugs which are commonly used to secure counter-irritation are witch hazel, alcohol, chloral, iodine, eucalyptus oil, chloroform, cajuput, rosemary, and menthol. Some of the unofficial substances which have been applied in this way are borneol, fenchone, abrin, horseradish, garlic, onion, cedar oil, and amber oil. Almost any volatile oil can serve the purpose.

STERNUTATORIES

There should be mentioned at this point the **sternutatories** or **errhines**, in which irritation is utilized in the nasal passages to secure mild reflex stimulation of the medullary centers, local stimulation, and an alteration in the secretions. The method was formerly quite common but is now almost obsolete. **Snuff** (tobacco) and saponins were the usual agents, but ipecac, euphorbium, ginger, capsicum, cubeb, etc., are efficient.

ESCHAROTICS

Escharotics (*corrosives*, *caustics*, *cauterizers*) destroy tissue by reacting chemically with the protein, the mass of necrosed cells forming a scab or "eschar." If the protein is dissolved, there is considerable penetration and a soft scab, making it difficult to control the amount of action; but if the protein is merely coagulated, the process is self-limiting to some extent. The amount of corrosion can be graduated by changing the concentration or the area over which it is spread, depending upon the individual caustic used.

This class of drugs includes the strong acids and alkalies, metallic salts, the halogens, phenol, alkaline salts, radium and X-ray, etc. The members are *used* (1) to cauterize snake bites; (2) to remove warts, corns, tumors, etc.; (3) to destroy nerves in teeth; (4) to remove hair (depilatory); (5) to promote scab formation and healing.

The application of caustics to mucous membranes, as in swallowing them accidentally or purposely, gives rise to *harmful effects* which are more or less uniform for the whole class of irritants. Those which do not destroy tissue cause nausea, vomiting, and diarrhea, with pain in the stomach and intestines and extensive secondary reactions upon the circulation and nervous system. In addition to these effects, the caustics usually cause excretion of blood and tissue debris with the vomit and stools, and the destruction of cells may even lead to perforation of the intestinal or stomach walls. The secondary symptoms, on account of the severity of corrosion, are much more important. Death may be caused by severe shock, by infective processes which are often to be expected, or by exhaustion and collapse. Delirium and convulsions may often accompany the poisoning. The treatment consists in administering an antidote, in evacuation, and in symptomatic measures.

1. The Alkalies

Sodium Hydroxide (Caustic Soda), U.S.P., B.P. Not less than 90 per cent of NaOH.

Potassium Hydroxide (Caustic Potash), U.S.P., B.P. Not less than 85 per cent of KOH.

Solution of Potassium Hydroxide, N.F., B.P. Dose: 1 cc., 15 minims, N.F.

Sodium Carbonate (Sal Soda, Washing Soda), B.P. $Na_2CO_3 \cdot 10H_2O$.

Monohydrated Sodium Carbonate (Exsiccated Sodium Carbonate), U.S.P., B.P. Dose: 0.25 Gm., 4 grains, U.S.P.

Potassium Carbonate (Salt of Tartar), U.S.P., B.P. K_2CO_3. Dose: 1 Gm., 15 grains, U.S.P.

The caustic alkalies destroy tissue by forming salts with the proteins, saponifying the fats, and dehydrating the protoplasm. They penetrate rapidly because of the solubility of the salts produced, forming a soft scab and giving rise to considerable pain, so that they are hard to confine to a prescribed area and are not desirable caustics. Mixing with lime, as in London (NaOH) and Vienna (KOH) pastes, gives much more satisfactory materials but never entirely so. They are rarely used in medicine to remove warts, corns, small tumors, etc., the potassium compound usually being preferred. Both are occasionally employed as detergents in surgery; in dilute solution, as antidotes for acid poisoning; and as antacids and antilithics.

In case of poisoning by the strong alkalies, the symptoms are those of any corrosive, which will be described under sulfuric acid. The dilute acids, as citric, acetic, or tartaric, are the best antidotes.

Since the **carbonates** depend for causticity on the hydroxides formed by hydrolysis, they are naturally less active. They may be used for the same purposes externally and are preferable for internal administration. Baths for certain skin diseases frequently contain sodium carbonate as an irritant, to remove horny layers and to relieve itching by counter-irritation.

2. Acetic Acid

Acetic Acid, U.S.P., B.P. 36 to 37 per cent of $CH_3{\cdot}COOH$.

Glacial Acetic Acid, U.S.P., B.P. Not less than 99 per cent $CH_3{\cdot}COOH$.

Diluted Acetic Acid, U.S.P., B.P. 5.7 to 6.3 per cent. Dose: 2 cc., 30 minims, U.S.P.

Trichloracetic Acid, U.S.P., B.P. $CCl_3{\cdot}COOH$.

Applied to the skin, glacial acetic acid produces irritation, inflammation, and finally blistering but corrosion only of the upper layers. It compares well with the strong mineral acids in caustic effects on mucous membranes, since poisoning may even result in hemorrhages or perforation of the stomach walls. The diluted acid may be ingested without any other action than an irritant stimulation, although long-continued use may give rise to gastric disturbances, loss in weight, and loss of appetite.

Acetic acid is commonly *employed* as a flavor, a solvent, a condiment, and as a preservative for foods. The strong acid was formerly popular for purposes of cauterizing septic wounds, ringworm, warts, corns, etc., but has been discarded for trichloracetic acid, which is more easily confined, gives but little pain, and is fairly efficient. Acetic acid is sometimes applied as a counter-irritant for contusions; as an anhydrotic in excess local perspiration; as a cooling application or sialagogue in fevers; as an antiparasitic; as a styptic and antiseptic in small hemorrhages, even in the lungs (inhalation) and in the uterus after parturition. Inhaled, irritation of the air passages is sufficient to give strong reflex stimulation of the vital functions, useful in narcotic poisoning, fainting, and collapse. Added to enemas, the irritation increases efficiency of purgatives. Vinegar is usually the best available antidote for poisoning by caustic alkalies. Like its salts, acetic acid alkalizes the blood and other body fluids (see acetates).

Trichloracetic acid, in addition to employment as escharotic, is applied to tubercular larynx for the relief of pain, being regarded by some as superior to lactic acid and other remedies.

3. Nitric Acid

Nitric Acid (*Aqua Fortis*), U.S.P., B.P. 67 to 69 per cent HNO_3.

This common acid was formerly much *used* to destroy abnormal growths but has been replaced by more useful substances because it causes great pain, stains tissue, and may leave a scar. Diluted, it may be, and occasionally is, employed like other acids in hypersecretion, as antiseptic, refrigerant, stomachic tonic, and cholagogue. For the last purpose, aqua regia (nitric and hydrochloric acids) was once very popular.

Toxicologically, nitric acid is like caustics in general, but the fumes from it are peculiarly dangerous because of delayed effects. These are due to nitrogen peroxide, formed whenever the acid acts as an oxidizing agent, which happens in contact with most organic matter. We shall note these effects when we have occasion to discuss the oxides of nitrogen.

4. Lactic Acid

Lactic Acid, U.S.P., B.P. A mixture of the acid and its anhydrides equivalent to 85 to 90 per cent of $CH_3{\cdot}CHOH{\cdot}COOH$.

It is similar to acetic acid in its effects but somewhat milder. It has become a popular application to malignant ulcers, to diphtheric membranes, and particularly to tubercular larynx. It was at one time erroneously administered as a hypnotic.

5. Chromic Acid

Chromium Trioxide (Chromic Acid or Anhydride), U.S.P., B.P. CrO_3.

Chromic acid is corrosive, hygroscopic, and antiseptic, precipitating albumin and hardening tissue. It is used as a caustic for ulcers and chancres; in solution as an antiseptic for mucous membranes, especially the urethra (1:5,000); as an astringent (5 per cent) for excessive perspiration, particularly of the feet. It has also been recommended as an antiparasitic.

The other chromium compounds are of minor importance in medicine but are often sources for *industrial poisoning.* The principal effects after ingestion are corrosion of the alimentary tract and kidneys, while chromate dust in the arts can cause ulcers, dermatitis, and nephritis.

Other Escharotics

Oxalic acid is of toxicological importance because it is sufficiently caustic to give gastro-enteritis and because it is often mistaken for non-poisonous salts which have similar crystalline form. After absorption, it generally produces convulsive symptoms and finally collapse. Calcium salts are the best antidotes.

Osmic acid and uranium nitrate have also been applied as caustics. The former is very expensive, and the latter is dangerous.

Of the heavy metals, salts of silver, mercury, and zinc are used, those of iron and copper to a lesser extent. Radium is of unique importance, as is also X-ray. Salicylic, sulfuric, and hydrochloric acids, ammonium hydroxide and lime, phenol, resorcin, chrysarobin, arsenic oxide, etc., are also in this class.

DEPILATORIES

These are agents which destroy superfluous hair. This can be done by radiotherapy or electrolysis which have several disadvantages. Escharotic agents are effective but no more so than is shaving, and, in addition, they may cause an eczema or other harmful effects after frequent application. Their use should be limited to those cases where shaving is impossible. The principal agents used are caustic alkalies and particularly the basic sulfides of calcium, strontium, and barium.

Thallium salts, especially the acetate and sulfate, have been used locally in ointment for destroying hair, but most authorities regard this as very dangerous practice. Indeed, commercial preparations of thallium for this purpose have caused many poisonings and deaths, and druggists should refuse to handle them.

Internally these salts give far-reaching effects of a very serious nature. Like those of lead poisoning, the symptoms are quite varied and sometimes indefinite, probably by selective action on all forms of nervous tissue. Even in infinitesimal doses they may give rise to untoward effects, and two or three doses may lead to retrobulbar paralysis and death. There have been more than 1000 recorded cases of poisoning and at least fifty deaths. The use of thallium as poison for rodents was the cause for some of these.

Thallium salts have been employed in recent years for treating ringworm of the scalp in children by giving a single dose of 0.008 gram (1/8 grain) per kilogram of body weight. The hair on the head, but not elsewhere, falls out in about two weeks and begins to grow back again in about a month. A second dose of thallium must not be given within a few months, since it is accumulative. The margin of safety is very small, and many practitioners consider radiotherapy safer and more efficient in the treatment of ringworm.

When poisoning does occur, the treatment is usually sodium thiosulfate intravenously (1 gram twice a day) and subsequently 2 grams of sodium iodide intravenously, with symptomatic therapy as indicated.

ASTRINGENTS

Astringents are drugs which contract tissue, usually by precipitating the proteins. Applied to animal matter, they coagulate the protoplasm, giving a superficial layer of hard, shrunken cells, preventing secretion, protecting the parts beneath, and lessening infection by creating a poor medium for bacterial growth. They may, therefore, be used (1) to check secretion and lessen diarrhea; (2) to allay inflammation; (3) to stop bleeding; (4) to promote healing by mild irritation; (5) to arrest the growth of micro-organisms; and (6) to harden tissue.

The principal astringents are acids, metal salts, tannins or vegetable astringents, and strong solutions which act by osmosis to deprive the cells of fluid. The metals vary in irritation from astringency to causticity in about the order: lead, aluminum, iron, zinc, copper, silver, tin, mercury. The organic acids, nitric, sulfuric, and hydrochloric, when combined with the metals, vary in the order given, so that almost any desired degree of action may be obtained by the proper combination.

Thus, mercuric chloride is typically caustic; while lead acetate is predominantly astringent; silver nitrate, intermediate.

1. The Vegetable Astringents

Tannic Acid (Tannin, Gallotannic Acid), U.S.P., B.P. A tannin usually obtained from nutgall. Dose: 1 Gm., 15 grains, U.S.P.

Glycerite of Tannic Acid (Glycerin of Tannic Acid), U.S.P., B. P.

Lozenge of Tannic Acid, B.P.

Tannic Acid Ointment, U.S.P., B.P.

Gallic Acid, N.F. $C_6H_2COOH(OH_3)$ 1:3:4:5. Dose: 1 Gm., 15 grains.

Styptic Collodion, N.F.

Acetyltannic Acid (Acetannin, Tannyl Acetate, Tannigen), U.S.P., N.R. A product obtained by acetylization of tannic acid. Dose: 0.6 Gm., 10 grains, U.S.P.

Albumin Tannate (Albutannin), U.S.P. Dose: 2 Gm., 30 grains.

Protan, N.R. A combination of tannin and casein. Dose: 1 to 2 Gm.

The tannins or tannoids are a group of substances obtained from various sources and having similar properties, all like tannic acid from nutgall. With the exception of the latter, their constitution is unknown. Some of them seem to be glucosidal, others not. Most of the tannins have astringent properties, which for our purpose constitutes a bond of union in classification. The action of tannic acid once described, we need but note the minor differences encountered with the others.

Applied to animal tissue, tannic acid *precipitates the proteins* in combinations which dissolve but slowly in excess of the protein. The tissue becomes harder and shrinks in volume, so that bleeding is prevented, secretions and excretions are reduced, inflammations are allayed by the protective coating, and, since the solubility of the precipitate causes some irritation, healing is promoted. Tannic acid has a bitter, "inky" taste, caused by the astringent action, which also occurs throughout the alimentary tract until the compound is decomposed by the alkaline intestinal secretions into gallates. These secretions are reduced and the walls are protected by a thin film of precipitated protein until the tannin is hydrolyzed, thus rendering the stools harder and counteracting diarrhea. There is, however, little effect upon peristalsis. Excessive amounts of tannin may be quite irritating, causing some nausea, vomiting, and diarrhea, and there is a tendency to interfere with absorption of digested food, while continuous ingestion of small amounts may be deleterious by causing inflammation and prevention of adequate digestion. Furthermore, some persons seem particularly susceptible even to small doses.

Tannic acid is *used* as a local application to the skin (5 to 20 per cent) or to any accessible mucous membrane (1 to 5 per cent) to reduce excessive secretion, to harden tissue, to stop bleeding and reduce inflammation, or to arrest hemorrhage.

One of the most valuable applications is in the treatment of extensive burns. For this purpose a 2.5 to 5 per cent solution in water is employed as lotion, spray, or bath. The absorption of proteins is prevented; toxemia is lessened; pain is relieved; loss of body fluid is decreased; the danger of secondary infection is lessened; formation of scars becomes less marked; and the firm, protective coating forms a scaffold for growth of new tissue. The mortality and morbidity from serious burns are said to be notably reduced. The value in superficial burns is much less apparent, since healing may be retarded. The simultaneous application of silver nitrate in 10 per cent solution seems to improve the effectiveness of tannic acid on burns.

Internally it has been popular for centuries as a remedy in diarrhea and in various diseases characterized by this condition. For the purpose, the liability of gastric derangement and decomposition in the upper intestines before therapeutic results have been gained, indicates a need for the substitution of the vegetable drugs containing tannin or of the chemical derivatives. Since tannic acid will precipitate most of the common alkaloids, except morphine, and many of the metal salts, it is employed largely as antidote in case of poisoning by such substances. The precipitates so formed, being gradually dissolved, must be removed promptly. A few of the tannin drugs are employed as astringent bitters for stomachic action and as anthelmintics for infestation by threadworms. Recently tannic acid has been applied in the treatment of peptic ulcer.

Gallic acid is devoid of astringent or irritant qualities and is readily absorbed, oxidized, and excreted without exerting any systemic action, so that it is not advantageously applied like tannic acid.

There are a large number of *drugs* which are dependent upon **tannin content** for activity and preferred where this must be extended very far into the intestinal tract, because the presence of colloids renders the tannin more slowly dissolved. There is really no reason for there being so many of them, as one or two would be amply sufficient for every purpose. The most popular are krameria, gambir (catechu), nutgall, and kino. Even these drugs are more or less disadvantageous as intestinal astringents, and this has led to the introduction of *chemical derivatives* of tannic acid which are claimed to be free from the drawbacks. Acetyltannic acid and albumin tannate have been given pharmacopœial recognition, and tannocol (gelatin tannate) has some popularity. They are presumed to be slowly soluble in the gastric contents but readily decomposed in the intestine to give astringency. The principal standard by which they are judged is the speed of solution under various conditions, with the proviso that all active material must be soluble in sodium carbonate.

The list below gives the official drugs that contain tannin or similar substances which place them in this class. All of them are applied locally as astringents and styptics for nose-bleed, hemorrhoids, ulcers, abscesses, and skin diseases or as gargles or mouthwashes in various conditions. Internally, some of them are administered as stringent bitters, and all as adjuvant remedies in diarrhea and dysentery. Witch-hazel preparations, especially the water, are highly esteemed as applications to sprains and bruises and in the pains of rheumatism and gout.

Krameria (Rhatany), N.F., B.P. The dried root of *K. triandra* (Peruvian Rhatany), or of *K. argentea* (Para or Brazilian Rhatany) (*Leguminosæ*). Dose: 1 Gm., 15 grains, N.F.

Fluidextract of Krameria, N.F. Dose: 1 cc., 15 minims.

Tincture of Krameria, B.P.

Extract of Krameria, B.P.

Lozenge of Krameria and Cocaine, B.P.

Gambir (Pale Catechu), N.F., B.P. The dried aqueous extract prepared from the leaves and twigs of *Ourouparia Gambir* (*Rubiaceæ*). Dose: 0.5 Gm., 8 grains, N.F.

Compound Tincture of Gambir, N.F. Dose: 2 cc., 30 minims.

Tincture of Catechu, B.P.

Hamamelis Leaves (Witch-hazel), N.F., B.P. The dried leaf of *H. virginiana* (*Hamamelidaceæ*). Dose: 2 Gm., 30 grains, N.F.

Hamamelis Water (Solution of Hamamelis, Witch-hazel Extract), N.F., B.P.

Fluidextract of Hamamelis Leaves, N.F., B.P. Dose: 2 cc., 30 minims, N.F.

Nutgall (Galla, Aleppo or Smyrna Galls), U.S.P. Galls from the young twigs of *Quercus infectoria* and other allied species of *Q.* (*Fagaceæ*). Dose: 0.5 Gm., 8 grains.

Nutgall Ointment, U.S.P.

Tincture of Nutgall, N.F. Dose: 4 cc., 1 fluidrachm.

Kino, U.S.P. The dried juice from the trunk of *Pterocarpus Marsupium* (*Leguminosæ*). Dose: 0.5 Gm., 8 grains.

Tincture of Kino, U.S.P. Dose: 2 cc., 30 minims.

Castanea (Chestnut Leaves), N.F. The dried leaf of *C. dentata* (*Fagaceæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Castanea, N.F. Dose: 4 cc., 1 fluidrachm.

2. Zinc

Zinc Acetate, U.S.P. $Zn(CH_3{\cdot}COO)_2{\cdot}2H_2O$.

Zinc Chloride, U.S.P., B.P. $ZnCl_2$.

Zinc Oxide, U.S.P., B.P. ZnO.

Zinc Oxide Ointment (Zinc Ointment), U.S.P., B.P.

Paste of Zinc Oxide (Lassar's Plain Zinc Paste), N.F.

Soft Paste of Zinc Oxide (Unna's Soft Zinc Paste), N.F.

Hard Paste of Zinc Oxide (Unna's Hard Zinc Paste), N. F.

Paste of Zinc Oxide with Salicylic Acid (Lassar's Zinc Paste with Salicylic Acid), N.F.

Compound Paste of Zinc Oxide, B.P.

Gelatin of Zinc (Unna's Paste), B.P.

Zinc Permanganate, N.R. $Zn(MnO_4)_2{\cdot}6H_2O$.

Zinc Phenolsulfonate (Zinc sulfocarbolate), N.F. $Zn(C_6H_5{\cdot}OSO_3)_2{\cdot}6H_2O$. Dose: 0.125 Gm., 2 grains.

Zinc Stearate, U.S.P., B.P. An impure salt containing variable proportions of zinc palmitate.

Ointment of Zinc Stearate, N.F.

Zinc Oleate Ointment, B.P.

Zinc Sulfate (White Vitriol), U.S.P., B.P. $ZnSO_4{\cdot}7H_2O$. Dose: 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Compound Powder of Zinc Sulfate, N.F.

Prepared Calamine, N.F. Native zinc carbonate, calcined at a moderate temperature.

Calamine Lotion, N.F.

Phenolated Lotion of Calamine, N.F.

Ointment of Calamine (Turner's Cerate), N.F.

Calamine Liniment, N.F.

The element zinc is apparently a normal and probably essential constituent of the human body, but its function is unknown. Zinc salts vary from astringents to corrosives according to the acid radical and the concentration. The chloride is a powerful caustic, because of its hydrolysis and its strong attraction for water, but much pain is caused, and the tissue destruction is quite extensive. The soluble compounds, when given by mouth, produce more or less violent irritation and all the symptoms of gastro-enteritis and in sufficient amounts can cause serious poisoning and even death. There is but little absorption from the alimentary canal, so that systemic effects by mouth are rare. Intravenously, zinc causes a paralyzing action upon the nervous system and muscles, which is merely of scientific interest. Long-continued ingestion by animals does not appear to give untoward symptoms, so that no danger is indicated for exposure.

The sulfate causes prompt emesis and is usually preferred to copper sulfate, since it is almost as efficient and less irritating. With the chloride, it is *employed* as an astringent and antiseptic lotion in eye washes and for urethral injection. The phenolsulfonate and acetate are less often used in the same way, the latter being mild and the former having no advantage. The insoluble compounds, which are feebly astringent and antiseptic, find their most useful application as dusting powders for skin diseases, as protectives and mild local sedatives. The stearate, which is smoother than the oxide or carbonate but probably no more efficient, has come into prominence as a source of poisoning after promiscuous use as an infant dusting powder. The chloride has been employed to cauterize malignant growths, because it destroys the tissue with considerable penetration and the eschar heals well, although the pain is greater than with some other corrosives.

There is no indication for the *internal administration* of zinc salts except for local action in the alimentary tract, but the oxide was used for years and is still infrequently prescribed, in various diseases of the brain, under the mistaken impression that it is sedative to the higher nerve centers. The proposal to use zinc as a substitute for other elements in syphilis has met with little favor.

The *toxicology* of zinc is relatively unimportant. Large doses may cause more or less severe gastro-enteritis, which is treated in the usual way. In the arts, zinc and brass workers are frequently subject to attack by "brass-founders' ague," consisting of intermittent chills and fever, which have been attributed to zinc. There is no direct evidence that this metal is responsible, and the possibilities are that the poisoning is caused by something else, probably lead or arsenic.

3. Aluminum

Alum (Purified Alum), U.S.P., B.P. Aluminum potassium sulfate, $AlK(SO_4)_2 \cdot 12H_2O$, or aluminum ammonium sulfate, $AlNH_4(SO_4)_2 \cdot 12H_2O$.

Exsiccated Alum (*Alumen Ustem,* Dried or Burnt Alum), U.S.P.

Glycerin of Alum, B.P.

Aluminum Sulfate, N.F. $Al_2(SO_4)_3 \cdot 18H_2O$.

Aluminum Chloride, N.F. $AlCl_3 \cdot 6H_2O$. Dose: 0.3 Gm., 5 grains.

Solution of Aluminum Chloride, N.F.

Solution of Aluminum Acetate (Burow's Solution), N.F.

Solution of Aluminum Subacetate, N.F.

Alumnol, N.R. Aluminum betanaphthol disulfonate, $Al_2[(C_{10}H_5OH)(SO_3)_2]_3$.

Aluminum salts precipitate proteins and, in concentration, have irritant or caustic effects. Dried alum is hygroscopic and, therefore, more caustic than the others. In the alimentary canal the astringency predominates, unless large amounts are ingested, when the irritant action causes nausea, vomiting, and occasionally diarrhea. Aluminum is absorbed very slowly and, although it is even more slowly excreted from storage in the liver, kidneys, muscles, and pancreas, there is never any other action than gastrointestinal irritation when administered by mouth. Injected hypodermically, serious poisoning may result, but it is of no practical importance. The warm debate over harmfulness after continued absorption of small quantities for long periods of time, as in the use of alum baking powders, cannot be said to have been settled, but any injurious action must be of very minor significance. A similar statement might be made about the alleged danger, chiefly of cancer, from the use of aluminum vessels in cooking.

Aluminum salts are infrequently administered for diarrhea but mostly limited to local application externally. They are *used* as astringents, styptics, and antiseptics, and exsiccated alum is a mild caustic. Alum is sometimes given in large doses (4 grams or more) as an emetic, but it is less reliable than the sulfate of zinc or copper.

A number of *new compounds* have been introduced into medical practice from time to time, although none of them seems to survive long. Besides alumnol, the salicylate (salumin), tannate (tannal), gallate (gallol), borotartrate (boral), borotannate (cutol), acetotartrate (alsol), and potassium aluminum salicylate (alkasal) are among those which have been suggested and used. The hydroxide is claimed to be an excellent remedy for gastric ulcer.

4. Lead

Lead Acetate (Sugar of Lead), U.S.P., B.P. $Pb(CH_3COO)_2{\cdot}3H_2O$.
Solution of Lead Subacetate (Goulard's Extract), N.F., B.P.
Diluted Solution of Lead Subacetate (Goulard or Lead Water), N.F., B.P.
Cerate of Lead Subacetate (Goulard's Cerate), N.F.
Suppositories of Lead with Opium, B.P.
Lead Monoxide (Litharge), N.F., B.P. PbO.
Plaster of Lead Oleate (Diachylon Plaster), N.F., B.P.
Ointment of Lead Oleate (Diachylon or Hebra's Ointment), N.F.

Lead compounds have very little *action* upon the intact skin, but, applied to mucous membranes, they precipitate a thin layer of proteins which protect and promote healing. They have also little action upon bacteria. Absorption is quite slow but takes place more readily than with most of the metals except mercury. Continued action of lead on almost any surface will lead to slow absorption, independent of the solubility of the compound. The excretion is very much slower, although the metal quickly disappears from the blood to be deposited in all organs, chiefly the kidneys, liver, and bones. The elimination may continue for months and even years, by the bile and feces, the urine, saliva, milk, and sweat. The systemic action of lead, which is very little understood in spite of numerous and extensive studies, is mainly of toxicological importance and has no bearing on uses in therapy.

All of the salts possess astringent action and may be *applied* to bruises, burns, chronic inflammations, skin diseases, rhus poisoning, etc. The mild irritation abets the astringency in promoting healing and as counter-irritant. There is always danger of poisoning even from the intact skin, so that the treatment should never be long continued. *By mouth,* lead acetate is sometimes prescribed for diarrhea and catarrh of the intestines, but this does not seem advisable. The opium of the old lead-laudanum lotion (L.L.L.) is superfluous. Lead itself is sometimes known as the opium of the skin.

The intravenous or intramuscular injection of lead compounds as a treatment of inoperable and other cancers was highly recommended and often applied for several years. The percentage of benefits found was always low, and, although any treatment which can ameliorate or in any way improve this hopeless condition in the slightest degree must be welcome, the majority seem now convinced of the inadequacy of such a method.

Acute lead poisoning is of rare occurrence and presents merely primary and secondary symptoms of gastro-enteritis. Occasionally apparent recovery has been transformed to chronic poisoning because of the accumulation. Sulfates are antidotes but not exceptionally good.

Chronic poisoning is very common as an accidental accompaniment of contact in the arts, of smoke from factories, of lead pipes and vessels, and in hundreds of other ways. No one can be entirely free from possible lead poisoning. The subject is of immense importance, as attested by the large number of cases every year and by the voluminous literature on sources, symptoms, prophylaxis, and treatment. No extensive review can be given here, but the student is referred to texts on toxicology and to the periodical literature of the past few years. The symptoms are quite variable, the most important being nutritional and metabolic changes, with *anemia*, intestinal cramps (*lead colic*), muscular paralysis (*drop wrist*), brain derangements, *constipation*, rheumatic pains (*arthralgia*), emaciation, and loss of appetite. A blue line of lead sulphide on the gums (*lead line*) and black stools are also characteristic. The treatment, after removal of the cause, consists in diet and sanitation, with symptomatic remedies if indicated. Prophylaxis and regulatory laws are very necessary.

5. Copper

Copper Sulfate (Blue Vitriol, Bluestone), U.S.P., B.P. $CuSO_4 \cdot 5H_2O$. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 10 grains.

Copper Citrate, N.R.

Copper salts resemble those of zinc, giving astringent precipitates with proteins of mucous membranes and the abraded skin. In larger concentration they may irritate considerably or cause a destructive action on the tissues. When ingested in sufficient quantity, the irritation caused by them usually produces prompt emesis, while larger doses give the other symptoms of gastroenteritis, for which potassium ferrocyanide is useful as an antidote. There is very little absorption from the alimentary tract, and excretion is fairly rapid; consequently, systemic poisoning is of rare occurrence. Furthermore, copper salts are usually evacuated promptly by emesis, so that large doses can be taken without any effect, even upon the alimentary tract, except vomiting. Although copper is not toxic to higher plants and very little to bacteria, the algæ and fungi are quite susceptible. Less than one part per million of copper sulfate will destroy such vegetation in water.

The citrate and sulfate are *used* as astringents and caustics for affections of the mucous membranes, particularly of the eye and urethra. They appear to present no advantage over silver compounds. Copper sulfate is a rapid and effective emetic without much nausea, but it is irritating and must be removed if it fails to act. It is especially indicated in such capacity in phosphorus poisoning, where it also acts as an antidote. Rarely, copper salts are employed in small doses for diarrhea.

Beginning with the discovery that minute amounts of copper will greatly increase the efficacy of iron in blood regeneration, extensive studies of metabolism have assigned this element to an essential role. There now seems little doubt that copper is normally present in the body, even if in extremely small amounts, most of it apparently in the blood. The only function that can definitely be attributed to it at present is in the formation of blood, where it in some way assists the necessary iron. In spite of this knowledge, it is very doubtful if copper salts are ever needed in the therapy of anemia.

Other Metals

The successful application of zinc, copper, lead, and aluminum in therapy has naturally induced attempts to utilize the compounds of other metals. Nickel, cobalt, cadmium, titanium, molybdenum, zirconium, gallium, samarium, etc., have been investigated but with no success.

Tin was at one time used for epilepsy, being one of the many remedies for this disease which have been discarded. It is, however, not readily absorbed, and the small amounts present in some canned goods do not cause toxicity. The symptoms of poisoning from tin are similar to those from lead without the accompanying accumulation.

The salts of iron, silver, mercury, etc., are astringent to corrosive, but they are chiefly used for other purposes.

Other Astringents

Tannin-containing drugs, which are occasionally depended upon for astringent action as secondary to a more useful property, include tea, rhubarb, pomegranate, alstonia, cinnamon, and serpentary.

Styptics or **hemostatics** frequently depend for their value upon a vasoconstriction instead of astringency, although the latter term is applied to them by some. Among the drugs of this class are epinephrine, ephedrine, cocaine, and tyramine. Ergot, pituitary, cotarnine, hydrastis, and ipecac are also administered internally with the object of controlling bleeding at various points.

ACTING LOCALLY—ON THE CAUSE OF DISEASE

ANTIPARASITICS

Since a pathological parasite is any organism that attacks or preys upon the animal body, an **antiparasitic** or **parasiticide** should theoretically be any drug that combats such an effect. The class would then include materials for flies and mosquitoes, ticks, lice, intestinal worms, fungi, and bacteria. Practically, however, the bactericides and anthelmintics (against worms) are usually segregated, because the remedies used are generally unified, and insecticides are commonly not given any place in therapy.

Commercial insect powders contain a large number of substances, of which pyrethrum, naphthalene, camphor, hellebore, tobacco, arsenic, mercuric chloride, cedar oil, menthol, and eucalyptus are examples.

The *common parasites* for which remedies are necessary are pediculi (lice), tinea, and scabies (itch). In addition might be mentioned the amebae that infect the intestinal tract. The usual method of treatment is by ointments or lotions of sulfur, tar, chrysarobin, mercury, oils, balsams, or phenols.

1. Sulfur

Sublimed Sulfur (Flowers of Sulfur), U.S.P., B.P. Dose: 4 Gm., 1 drachm, U.S.P.

Sulfur Ointment, U.S.P., B.P.

Compound Sulfur Ointment (Wilkinson's Ointment, Hebra's Itch Ointment), N.F.

Alkaline Sulfur Ointment, N.F.

Washed Sulfur (Sulfur Lotum), U.S.P. Dose: 4 Gm., 1 drachm.

Precipitated Sulfur (Lac Sulfuris, Milk of Sulfur), U.S.P., B.P. Dose: 4 Gm., 1 drachm, U.S.P.

Confection of Sulfur, B.P.

Sulfurated Potash (Liver of Sulfur), U.S.P., B.P. A mixture of potassium polysulfide and thiosulfate containing about 13 per cent of sulfur.

Solution of Sulfurated Lime (Vleminckx Solution or Lotion), N.F.

White Lotion (Lotio Sulfurata), N.F.

Sulfur itself is entirely inert but is slowly converted by certain proteins of the skin and mucosa into hydrogen sulfide or its salts, which are more or less irritating. After oral administration, such a change to sulfides does not take place in the stomach and upper intestines, but it becomes great enough in the large intestine to stimulate peristalsis of the latter and to promote the production of a soft stool. Sulfides cannot replace sulfur for this action because they are readily absorbed and toxic. All sulfur compounds are inimical to parasites.

Sulfur ointments and soaps have long had a high reputation for treating scabies, although there now seems some tendency to replace it by balsam of Peru. Parasitic and other *skin diseases* and baldness are treated in the same way, because of specific action upon the organisms and for the mild irritation, which allays inflammation and promotes epithelial growth. Sulfur is also said to be a local sedative in itching skin diseases and is sometimes applied to the skin in substance for the relief of neuralgia. It is given *internally* for boils and carbuncles, for skin diseases, and by the laity as a blood purifier. The mild laxative effect is often useful to soften the stools in order to prevent irritation, as in piles. Injections of sulfur hypodermically constitute a source of artificial fever used in treating various diseases. This matter will be discussed later. The sulfides are unique caustics for removing hair, particularly crude calcium sulfide. They are also used as antidotes for metal poisonings and more often employed in the form of sulfide baths to promote elimination in chronic poisonings. They have also been suggested as antidotes for cyanides, on the basis of sulfocyanide formation. Sulfhydryl organic compounds (*e.g.*, thioglycerol) are recommended for local treatment of wounds.

After absorption, the sulfides cause *systemic effects* similar to those from hydrogen sulfide, but these are slow in appearing because of delay in penetration. The gas is a very poisonous substance which is nearly as rapid in producing death as hydrocyanic acid. With concentrations in the inspired air as low as 0.7 per cent, a person is almost certain to die within several hours, and double that amount is rapidly fatal. The symptoms are faintness, headache, coma, and death, with or without convulsions. The treatment is fresh air, artificial respiration, stimulants, and in general that for narcotic poisoning.

Thiosinamine was introduced as a sorbefacient for swellings and inflammations. It has been recommended to eliminate dermatitis after arsphenamine injection. Other sulfur compounds (hyposulfite) have been used in the same way and also to counteract poisoning by arsenic.

The element **selenium** has recently come into prominence as a source of poisoning in cattle, because it appears to be present in small amounts in grasses and grains in certain localities.

2. Ichthammol

Ichthammol (Sulfonated Bitumen, Isarol, N.R.), N.F., B.P. A viscous fluid obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate, and neutralizing the product with ammonia. Dose: 0.2 Gm., 3 grains.

Ichthammol Ointment, N.F.

Ammonium Ichthyolate, N.R. An aqueous solution derived from oily distillates of a fossiliferous bitumen found in Texas.

Hirathiol (Ammonii Sulfoichthyolicum), N.R. An aqueous solution of a synthetic product containing ammonium compounds of sulfur.

Ichthynate (Ammonium Ichthynate), N.R. An aqueous solution resulting from sulfonation of the tar-like distillate obtained from certain bituminous shales.

Thigenol, N.R. A solution of the sodium salts of synthetic sulfo-oleic acids, containing 2.85 per cent of sulfur.

The ammonium compounds of these sulfur-containing acids, obtained from various mineral and fossil shales, have been used very extensively in medicine, being originally introduced under the title of ichthyol. The latter is but slightly irritating to the skin and but little more to mucous membranes. Large doses may cause some diarrhea but generally no other poisonous effects. It is very mildly antiseptic, fairly emollient, and is said to be a vasoconstrictor to the vessels near mucous membranes.

Ichthyol has been *used* in 10 to 50 per cent ointment locally in skin diseases and inflammations and especially in gynecology to relieve pain and congestion. It has been recommended internally for a large variety of conditions, but the evidence is very unconvincing, and, for this reason, there seems a tendency to abandon its internal use. In tuberculosis it is claimed to increase appetite and strength, undoubtedly an exaggeration.

3. Sodium Thiosulfate

Sodium Thiosulfate (Sodium Hyposulfite), U.S.P. $Na_2S_2O_3 \cdot 5H_2O$. Dose: 1 Gm., 15 grains by mouth or intravenously.

Ampuls of Sodium Thiosulfate, N.F. Dose: 10 cc. (about 1 Gm.).

This salt was formerly much used as intestinal antiseptic and in blood infections. It is now infrequently employed to combat ringworm, parasitic skin diseases, and aphthous stomatitis. The notorious "athlete's foot" is successfully treated by a 20 per cent solution. The salt also has some popular reputation as a laxative.

Intravenously sodium thiosulfate is an effective antidote for some poisons. It is rather difficult at present to evaluate the method in many cases, but in any event the injection can do little harm. Cyanides, arsenic, mercury, lead, carbon monoxide, iodides, and bismuth have been combated in this way.

The use of sodium thiosulfate as a test for renal function is by some considered preferable to that of phenol red.

The **sulfite** has been applied like sulfurous acid to preserve food, including meat. Although there may be no particular harm from such a method and it is allowed within limits, the use on meat to make it appear fresh is certainly to be condemned.

4. Tar

Pine Tar (Tar, Pix Pini, Pix Liquida), U.S.P., B.P. A product obtained by the destructive distillation of the wood of *Pinus palustris* and other species of *Pinus* (*Pinaceæ*).

Syrup of Pine Tar, U.S.P. Dose: 10 cc., 2½ fluidrachms.

Pine Tar Ointment, U.S.P.

Rectified Oil of Tar, U.S.P. Dose: 0.2 cc., 3 minims.

Compound Ointment of Tar, N.F.

Juniper Tar (Oil of Cade, Empyreumatic Juniper Oil), U.S.P., B.P. The empyreumatic volatile oil obtained from the woody portions of *Juniperus Oxycedrus* (*Pinaceæ*).

Compound Liniment of Soft Soap, N.F.

Rectified Oil of Birch Tar, N.F. The pyroligneous oil obtained by the dry distillation of the bark and wood of *Betula alba*, rectified by steam distillation.

Tar contains phenols and other benzol derivatives which are all more or less antiseptic. Applied to the skin it is strongly irritating; continued application may lead to extensive inflammation. The local anesthetic properties of phenols may allay itching. On mucous membranes the irritation is more severe, so that it must be diluted. Tar is readily absorbed from most surfaces, sufficient to cause dark color in the urine and sometimes even to produce phenol poisoning, with acute nephritis, nervous depression, colic, vomiting, and diarrhea. Tar and coal tar have been used to produce typical cancers by making continued applications to the skin, especially of the rabbit's ear.

Tar has been *employed* for years as a local application for various kinds of skin diseases and wounds, but the conglomerate mixture is rightly being discarded in favor of the pure phenols naphthol and resorcinol. It has also been administered internally for skin diseases, apparently on the assumption that excretion of the components would act locally. It is still quite popular as an antiseptic ingredient and flavoring for cough mixtures and inhaled as a treatment for bronchitis; also, as a urinary and intestinal antiseptic. In some localities it is considered an excellent anthelmintic if given in large doses. For disinfecting feces, lavatories, etc., tar is efficient and cheap but has been largely replaced by chlorinated lime.

Cade oil and **oil of birch tar** are very similar to pine tar in source and properties and are used externally in the same way. They are usually considered more agreeable.

5. Chrysarobin

Chrysarobin, U.S.P., B.P. A mixture of neutral principles obtained from Goa powder, a substance deposited in the wood of *Vouacapoua Araroba* (*Leguminosæ*).

Chrysarobin Ointment, U.S.P., B.P.

Chrysarobin is strongly irritant to the skin, sometimes leading to swelling or even eruptions. It is absorbed readily but is also rapidly excreted as chrysophanic acid, an oxidation product, or unchanged. Large doses by mouth cause violent gastro-enteritis and nephritis. The effects have been ascribed to its reducing action which compares well with that of pyrogallol, used similarly. The skin and linen are stained a reddish brown, which can be removed with oxidizing agents or by solvents.

Chrysarobin is *used* as ointment in parasitic and other skin diseases but best in gelatin or watery solution, because fats hinder oxidation. It has been claimed as the only certain remedy in psoriasis, although it is certainly not a cure. Care must be exercised to keep the drug away from the eye, because it causes violent inflammation of the lids and may even render the lens opaque. It has also been employed as a caustic for warts. **Anthralin** (dihydroxy anthranol), a synthetic substitute, seems to be very efficient and certainly lacks some of the definite disadvantages of chrysarobin, much more so than the former neorobin.

6. Pyrogallol

Pyrogallol (Pyrogallic Acid), U.S.P. Trihydroxybenzene, $C_6H_3(OH)_3$ 1:2:3.

Lenigallol, N.R. Pyrogallol triacetate.

This phenol causes blackening of the skin and slight irritation which may produce an erythema after continued application. It is mildly caustic on abrasions or on mucous membranes. Care must be exercised that it is not used over too large an area, because absorption takes place easily from any surface. The reducing effect, which is a well-known chemical property, causes systemic actions on the blood which outweigh any phenol effect. The red cells are disrupted, allowing the hemoglobin to diffuse into the serum, where it is converted into brown methemoglobin. Nephritis, jaundice, and asphyxia result, and later death from uremic convulsions. The urine is colored brown or black independently of the presence of blood. The treatment of such poisoning must be merely symptomatic.

Pyrogallol has been *used externally* as an application in parasitic and other skin diseases, especially psoriasis, and to deodorize and disinfect foul-smelling excretions from ulcers. It is also an ingredient of hair dyes, in the application of which there is always the danger of poisoning. The local action may be referred to chemical reduction.

7. Larkspur

Larkspur Seed (Delphinium), N.F. The dried, ripe seed of *Delphinium Ajacis* (*Ranunculaceæ*).

Tincture of Larkspur, N.F.

Acetic Tincture of Larkspur, N.F.

The delphinium drugs have been used since prehistoric times as applications to combat head lice and other parasites and are components of many commercial mixtures for the purpose. Since the alkaloid, delphinine, is similar to aconitine in action, several cases of poisoning have occurred. The symptoms and treatment may be considered identical with those described under aconite.

8. Cocculus

Cocculus (Indian or Fish Berries), N.F. The dried ripe fruit of *Anamirta Cocculus* (*Menispermaceæ*).

Tincture of Cocculus, N.F.

Cocculus contains a very poisonous glucoside, **picrotoxin,** which has been the cause of a number of fatalities. The drug has been used to kill fish, which are then poisonous to man, or it is sometimes added to soft drinks to increase bitter taste. The chief characteristics of the poisoning are convulsions of medullary origin, respiratory exhaustion, high blood pressure and slowed heart, restlessness, and unconsciousness.

The small margin of safety precludes the *use* of picrotoxin to stimulate the medullary centers, but it has been administered empirically in epilepsy, chorea, poisoning by barbituric derivatives, and the night-sweats of tuberculosis, some with very doubtful results. The berries and preparations from them are employed in the form of ointments against lice, but naturally the method is dangerous.

9. Pyrethrum

Pyrethrum Ointment, N.R.

Pyrethrum, derived from species of *Chrysanthemum* and not to be confused with pellitory root, is perhaps the most common of ingredients in commercial insect powders. It is often applied for lice and administered for worms, but local reactions are a great deterrent.

Other Antiparasitics

Naphthalene and **paradichlor benzene** (dichloricide) are moth repellents and sometimes added to commercial mixtures for use against parasites.

Fluorides and fluosilicates (silicofluorides) are used against ants, roaches, moths, etc., being usually very effective. Sodium fluosilicate is also a promising spray in horticulture. Attempts have been made from time to time to introduce sodium fluoride into medicine, especially for exophthalmic goiter, but it gives general untoward effects, and there is always danger of poisoning. Although the element fluorine is normal in the body, chiefly in teeth and nails, excessive amounts lead to mottled or otherwise affected teeth. More than 2 parts per million in drinking water is probably thus injurious, while larger quantities may give serious symptoms.

There are a great number of drugs which are frequently applied as antiparasitics but chiefly for some other purpose. The metallic salts are sometimes of much service, especially those of mercury. Most of the volatile oils are distasteful or actually inimical to the parasites. Eucalyptus, cajuput, rosemary, nutmeg, camphor, and sassafras are among the more important. Being actively parasiticidal, the phenols are very effective. Besides tar and pyrogallol, a number of them are so applied, especially eugenol, phenol, thymol, cresol, creosote, betanaphthol, and resorcin. Among the other drugs employed in this way might be mentioned balsam of Peru, benzoin, cyanides, benzin, cinchona, boric acid, iodine, petroleum, and quassia.

ANTHELMINTICS

Anthelmintics (anti, against; helminthos, worm), **vermicides,** or **vermifuges** are agents used to kill or expel intestinal parasites, more specifically worms. The most important of these are tapeworms (*Tænia* species or *Bothriocephalus latus*), hookworms (*Anchylostomum duodenale* and *Uncinaria americana*), roundworms (*Ascaris lumbricoides*), and threadworms (*Oxyuris vermicularis*).

Active catharsis should theoretically suffice to carry out the parasites, but they have such a remarkable tenacity in holding their position in the intestines that drugs must be administered to paralyze or kill them. All of the remedies are more or less inimical to the patient, and one must exercise care in the dosage, remembering at the same time that they must be given in *maximum amounts* in order most efficiently to accomplish the result. The ideal anthelmintic would be poorly absorbed but poisonous to the worm in small doses.

In order to insure optimal *removal* of the worms, a preliminary fast is usually directed, although this may be detrimental by assisting absorption of the drug and by weakening the patient. The remedy is then administered on an empty stomach and followed after one hour, or accompanied, by an active purgative, because the worms are seldom killed but only temporarily paralyzed. The condiments, such as salt, onions, pepper, etc., are usually adjuvant and should be taken freely in the last meal.

The most valuable anthelmintics are carbon tetrachloride and tetrachlorethylene for hookworm, aspidium and pelletierine for tapeworm, oil of chenopodium and santonin for roundworm, arecoline for animals. Infection by oxyuris is generally treated by enema with astringents and bitters.

1. Halogen Derivatives

Carbon Tetrachloride, U.S.P., B.P. CCl_4. Dose: 2.5 cc., 40 minims, U.S.P.; maximum (caution) 3 cc.

Tetrachlorethylene, N.F. Dose: 3 cc., 45 minims.

By inhalation, carbon tetrachloride gives anesthetic effects similar to those from chloroform. Large doses by mouth may result in considerable absorption and subsequent fatty degeneration of the liver and kidneys, which can indirectly cause death. In therapeutic amounts, the quantity of absorption is almost negligible, and the only effect is a purgative action, occasionally some headache, giddiness, and nausea. Sometimes, however, for various reasons not well understood, much more finds its way into the blood stream to become a potential danger, and alcoholics seem particularly susceptible. The simultaneous administration of magnesium sulfate or the previous use of calcium salts and parathyroid have been proposed to counteract any tendency to poisoning. The danger is not great, since large amounts have been given without untoward effects, and records show a low percentage of toxicity.

Carbon tetrachloride is an excellent anthelmintic for the hookworm; one dose will eliminate 75 to 100 per cent of the worms, and, together with care to prevent reinfection, a second dose a month later will usually cure. Against other worms, the efficacy is not so great, although it is often recommended, even against the tapeworm.

Tetrachlorethylene is similar in physiological action but does not show much tendency to poisonous effects. It is probably considerably safer and just as efficient against hookworms, although it is somewhat less agreeable to take.

2. Santonin

Santonin, U.S.P., B.P. The inner anhydride, $C_{15}H_{18}O_3$, of santonic acid. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum, 5 grains.

Santonin is insoluble in water, therefore practically tasteless and unirritating, but in the alkaline intestine is converted to salts which are soluble. A small amount is always absorbed, while most of it is excreted unchanged in the feces, in spite of its solubility. The *systemic action* in small doses consists of a persistent yellow vision, and larger ingestion may cause severe intoxication. The symptoms are vomiting, diarrhea, kidney pains, hematuria, strangury, headache, muscular depression, convulsions, and collapse. The urine is colored yellow, changed to red by alkalies. In treating, the stomach should be evacuated, and symptomatic remedies administered. The most characteristic effect after therapeutic administration, and also in severe poisoning, is the disturbance of color vision; the sensitivity to the violet spectrum is reduced and to red or yellow is increased. Usually everything appears blue or violet first, then yellow.

Santonin has been *employed* since early times as a treatment for roundworms and other intestinal parasites. It is now administered in doses of ½ to 2 grains, with or followed by castor oil or some other cathartic. The tablets are quite popular but have the disadvantage of being mistaken for candy by children. It is presumed best not to have the stomach empty at time of taking, because absorption and poisoning might be increased. Santonin has been tried in other diseases without favorable result.

3. Aspidium

Aspidium (Male Fern, Filix Mas), U.S.P., B.P. The rhizome and stipes of *Dryopteris Filix-mas* (*Polypodiaceæ*).

Oleoresin of Aspidium, U.S.P. Dose: (caution) single dose a day 4 Gm., 1 drachm, U.S.P.; maximum 4 Gm.

Extract of Male Fern, B.P.

Aspidium owes its effects to several components closely related chemically, of which the most important is filicic acid, $C_{35}H_{38}O_{12}$. This compound seems to paralyze the muscles of the parasite by direct action. Oils are presumed to increase its absorption and thus give poisoning, but many have denied this and actually use castor oil as cathartic. There is always a chance for toxic effects even from small doses. The symptoms are diarrhea, headache, jaundice, anuria, vision derangements, delirium, muscular cramps, convulsions, and respiratory paralysis. If recovery takes place, it is only slowly, and the patient may have permanent injuries, such as blindness from spasm of the retinal muscles. The treatment would be symptomatic, mainly by respiratory stimulation.

Aspidium is most efficient against *tænia* but may also be used for the *hookworm.* The oleoresin is given in doses of about 2 to 4 grams, in capsules or emulsion, and not repeated. The maximum dose is somewhat debated, but in a healthy man 4 grams should be safe if an active cathartic is administered afterward; indeed, prominent practitioners recommend double this dosage.

4. Pomegranate

Pelletierine Tannate, U.S.P., B.P. A mixture of the tannates of several alkaloids obtained from pomegranate, *Punica Granatum* (*Granataceæ*). Dose: 0.25 Gm., 4 grains, U.S.P.; maximum 10 grains.

Decoctions and extracts of pomegranate have been used for years as worm remedies. The *administration* is quite disagreeable because of the tannin and other substances present, a disadvantage that has been obviated by the introduction of pelletierine. *Poisoning* may follow even small doses, and large ones cause gastro-enteritis, vision disturbances, convulsions, and profound coma.

The alkaloidal mixture is a fairly efficient remedy for *tænia,* sometimes for roundworms, given in doses of 2 to 10 grains and followed by a purge. Pomegranate is sometimes employed as an astringent like the other tannin drugs, because it contains a large amount (25 per cent) of this substance.

5. Oil of Chenopodium

Oil of Chenopodium (Oil of American Wormseed), U.S.P., B.P. A volatile oil distilled with steam from the fresh, over-ground parts of the flowering and fruiting plant of *Chenopodium ambrosioides* var. *anthelminticum* (*Chenopodiaceæ*). Dose: 1 cc., 15 minims, U.S.P.; maximum 1 cc.

Oil of chenopodium, a more recent drug, has been recommended as an anthelmintic against all kinds of intestinal parasites. In practically every case of therapeutic employment there occurs some minor side action, and frequently it causes some poisoning, the usual toxic effects being nausea, dizziness, tingling in the extremities, and persistent deafness. In case of very large doses, which have been infrequently encountered, the patient experiences the preceding effects, together with convulsions and extensive coma.

Oil of chenopodium seems to be the only successful drug in *roundworm* infection, in spite of the high reputation accorded to santonin. It is given in 1-cc. doses several times a day, without any special preparation of the patient and with castor oil or some other purgative after the last one. It is frequently administered alone or with other anthelmintics against tapeworm and hookworm, and the claim is often made that *oxyuris* and *trichocephalus,* more resistant than other worms, can be eradicated by the oil. Sometimes, also, it is employed in place of ipecac and emetine as a remedy in amebic dysentery.

6. Arecoline

Areca (Betel Nut), N.F. The dried, ripe seed of *A. catechu* (*Palmæ*). Dose: dogs 2 to 4 Gm., 30 to 60 grains; sheep 4 to 8 Gm., 1 to 2 drachms.

Arecoline Hydrobromide, N.F. $C_8H_{13}O_2N \cdot HBr$. Dose: 0.03 Gm., ½ grain subcutaneously for horses, or 0.0015 Gm., 1/80 grain per pound.

Areca is used chiefly in veterinary practice against tapeworm and roundworm. The alkaloid is more convenient and can be administered by injection.

7. Kamala

Kamala (Rottlera), N.F. The hairs obtained from the capsules of *Mallotus philippinensis* (*Euphorbiaceæ*). Dose: 8 Gm., 2 drachms; fowls 0.5 to 1 Gm., 8 to 15 grains.

This drug is employed against tapeworm in doses up to 12 grams, suspended in water or syrup. It is actively cathartic, so no additional agent of this kind is necessary. The natives also use it for a local application in scabies, and it has been applied successfully for ringworm.

Other Anthelmintics

Among the substances that are less important might be mentioned: spigelia (pinkroot), formerly a popular treatment for ascarides; pumpkin seeds, once considered a useful adjuvant but probably worthless; brayera (cusso or kousso), used for the tapeworm; butea seeds; embelia. Geraniol, a common alcohol in volatile oils, is claimed to be extremely efficient against hookworm, and hexylresorcinol is said to be excellent for treating any kind of infestation by worms.

Other substances described elsewhere, which are often used for this purpose, are thymol and betanaphthol. Oils of cajuput, turpentine, tansy, thuja, eucalyptus, and other volatile oils are similar to thymol. Among the numerous other drugs employed as anthelmintics, there may be mentioned chloroform, glycerin, acetone, tar, matricaria, convallaria, caulophyllum, eupatorium, camphor, croton oil, scammony, jalap, and other purgatives. Iron, tannin, quassia or other bitters, etc., are given in high enemata for *threadworms.*

ANTISEPTICS

The drugs used to combat micro-organisms we may call antiseptics, since this is the popular term. The substance may, however, merely suspend the vitality of the microbe, preventing it from growth, or it may kill the organism, thus permanently destroying its power to do harm. To the former class we should rightly apply the name antiseptic (against infection); to the latter, *germicide* or *disinfectant;* the last name is sometimes used to describe both classes. Since the question is simply one of degree in most cases and a preventive agent can be destructive in sufficient quantity, the term antiseptic is usually made to include any substance that will destroy or prevent infection by bacteria. In this connection, attention should be called to the fact that a drug that is labeled as an antiseptic must actually be germicidal when used according to directions; those entrusted with the enforcement of the Food and Drugs Act have made such a rule.

It is sometimes rather difficult to choose the most efficient antiseptic out of the hundreds of drugs that are more or less used under a variety of conditions. The *selection* in any particular case depends upon summation of several factors, the most important of which are the nature, strength, penetration, and toxicity of the substance in question; the susceptibility, position, and number of organisms; the time and temperature of exposure; the cost. No comparison can, therefore, be made between two antiseptics without considering all of these factors, a fact often forgotten during the discussion of merits of some new or old drug to be applied as an antiseptic.

The *ideal substance* for body application would be one that is destructive to the bacterial cell without irritating or harmfully affecting the host tissue in any way. The antiseptics which act upon proteins by chemical reaction would, of course, not answer this description, and others also do not fully meet this requirement, although it is difficult always to show the method of action. It can be stated generally that no antiseptics are harmless to the tissues and that they are selected with a view to least injury. Some seem to have a peculiar selection for certain organisms with minimum action upon other tissue; quinine in malaria, arsenic in protozoal infection, etc. Mixtures of compounds are often more effective than any one alone.

A complete list of all substances used as antiseptics would not accomplish any object. Among the most popular, in approximate order of strength under usual conditions, are mercuric chloride, silver nitrate, formaldehyde, chlorine, hydrogen peroxide, phenol, cresol, salicylic acid, boric acid, sulphurous acid, volatile oils. All irritants could be placed in the list. Naturally, those most poisonous to man by local action are also most bactericidal. For particular purposes the most important are:

Wounds—hydrogen peroxide, iodine, mercurochrome, chlorinated soda, borates, phenols.

Instruments—heat, phenols, mercuric chloride.

Skin diseases—chrysarobin, pyrogallol, naphthol, tar, resorcin.

Intestines—cresols, naphthols, salol, calomel, purgatives.

Urinary—methenamine, salicylates, santal oil, mandelates.

Pulmonary—balsams, volatile oils, creosote.

Rooms, etc.,—formaldehyde, sulfur dioxide, chlorine, phenol.

Water—chlorine, hydrogen peroxide, ozone, organic peroxides.

1. Borates

Boric Acid (Boracic Acid), U.S.P., B.P. H_3BO_3. Dose: 0.5 Gm., 8 grains, U.S.P.
Glycerite of Boroglycerin (Glycerin of Boric Acid), U.S.P., B.P.
Solution of Boric Acid, N.F.
Suppositories of Boroglycerin, N.F.
Boric Acid Ointment, U.S.P., B.P.
Sodium Borate (Borax, Sodium Pyro-, Tetra-, or Bi-borate), U.S.P., B.P. $Na_2B_4O_7 \cdot 10H_2O$.
Glycerin of Borax, B.P.
Honey of Borax, B.P.
Honey of Rose and Sodium Borate, N.F.
Sodium Perborate, U.S.P. $NaBO_3 \cdot 4H_2O$. Dose: 0.06 Gm., 1 grain.
Aromatic Sodium Perborate, N.F.

The *physiological actions* of boric acid and of borax are practically identical. They are very feebly germicidal but are distinctly antiseptic and cause little irritation. With doses up to 8 grains there is no systemic action, although absorption occurs readily. The excretion is rapid at first but slows down after the first 75 per cent, so that 4 or 5 days are usually required for completion. This excretion is mostly by the kidneys, partly by the milk and sweat. Larger amounts cause acute poisoning, which may be encountered also after extensive local application, the symptoms being those of alimentary irritation and nephritis, with visual disturbances, muscular incoordination, fall in temperature, and collapse. Necropsy shows extensive fatty degeneration. Small doses (1 to 2 grams per day) continually may induce borism, characterized by disturbances in digestion, metabolism, and kidney action, loss of appetite, sleeplessness, headache, loss in weight, falling hair, eczema, swelling of skin, and muscular debility. Withdrawal of the drug generally removes the symptoms after several days.

All of the official boron compounds are *used* in solution, ointment, or substance as mild antiseptic applications to wounds, burns, ulcers, etc., but are not suited to disinfect. They may be applied on any accessible membrane, because they irritate very little. Powdered boric acid and sodium perborate may be employed as non-irritant dusting powders in surgery and in skin diseases, while borax is an ingredient of many insect powders. They have all been considered as emmenagogues although no specific action on the uterus is known. Borax has often been used as abortifacient in the face of almost certain poisoning. The derangement of metabolism causes loss in weight, so the borates have been recommended, 3 grams daily, for obesity, a procedure as unjustified as any that depends upon metabolic interference, such as dilute acids. Formerly borates were used as sedatives, especially in epilepsy, but have now rightly been discarded for this purpose. Borax tends to render the urine alkaline, and boric acid to make it more acid, actions that may be occasionally used. Both are good preservatives of foods, but their use has been prohibited by law in practically every country.

Sodium perborate with water gives hydrogen peroxide which can be used for germicidal purposes. It is chiefly applied locally for gingivitis (Vincent's angina, trench mouth) and for infections of the vagina.

2. Silver and Gold

Silver Nitrate (Argenti Nitras), U.S.P., B.P. $AgNO_3$. Dose: 0.01 Gm., 1/6 grain, U.S.P.; maximum 1/2 grain.

Toughened Silver Nitrate (Moulded or Fused Silver Nitrate, Lunar Caustic), U.S.P., B.P.

Strong Protein Silver (Strong Protargin, Protargentum, Protargol), U.S.P., N.R.

Mild Protein Silver (Mild Protargin, Argyn, Argyrol, Cargentos, Silvol, Solargentum), U.S.P., N.R.

Collargol (Colloidal Silver), N.R.

Lunosol (Colloidal Silver Chloride), N.R.

Neosilvol (Colloidal Silver Iodide), N.R.

Silver Citrate, N.R. $Ag_3C_6H_5O_7$.

Silver Lactate, N.R. $AgC_3H_5O_3 \cdot H_2O$

Silver Picrate, N.R. $C_6H_2(OAg)(NO_2)_3 \cdot H_2O$.

Sodium Gold Thiosulfate, N.R. $Na_3Au(S_2O_3)_2 \cdot 2H_2O$.

Triphal, N.R. Chiefly sodium aurothiobenzimidazole, $C_6H_3N{:}NHCSAu\text{-}COONa$.

Dilute silver nitrate causes redness and itching on the intact skin, but more concentrated solutions produce blisters, and the pure salt gives a white eschar which rapidly turns dark by reduction of the compound formed. On mucous membranes the action is much more severe, graduated from astringent to caustic depending upon the concentration. The caustic effect is due to superficial precipitation of protein material, which more or less limits its penetration, and it can be controlled readily by means of sodium chloride. The precipitate is somewhat soluble in excess protein so that the silver is absorbed in slight degree, being stored in the connective tissue as reduced silver. This causes the dark-gray or black color easily observable from the surface. The deposition, which is known as *argyria*, begins in the gums but soon extends over the whole body, especially the face, and may be produced by internal administration or local application of silver salts. The dark color of the skin is permanent and harmless except for the loss in social standing. Intracutaneous injections of 0.25 per cent potassium ferricyanide and 6 per cent sodium thiosulfate have been used to remove the pigmentation. Large doses of silver salts by mouth cause only symptoms of gastro-enteritis, seldom dangerous, as shown by the fact that survival from 30 grams has been recorded. Injected hypodermically, silver causes stimulation and then depression of the nervous system, with death from paralysis of the respiration and edema of the lungs; the heart is not greatly affected.

Silver nitrate is *employed* as a caustic for the easy removal of warts and other skin growths, diphtherial membrane, chancres, and ulcers and as astringent, local stimulant, and antiseptic for many infective diseases of mucous membranes. The application of a 2 per cent solution in the eyes of newborn infants to prevent gonorrheal infection is a routine procedure, and it is injected into the urethra to prevent or cure the same disease in adults. It has been given orally to secure astringency and asepsis in catarrhal conditions of the stomach and intestines, in gastric ulcer, for diarrhea, and as a sedative in nervous diseases. Except for local gastric disturbances, it is probably of little value for internal therapy. The sedative application is a relic of prehistoric times, probably derived from superstitions of the Arabs that silver (the moon) is related to the brain and lunacy.

The easy penetration of silver protein combinations has led to the introduction of a large number of commercial preparations of **colloidal silver,** which are not astringent and not corrosive. Some degree of antiseptic quality is retained which is not proportional to the content of silver but probably due to the amount of metal that is ionized. They are manufactured by dissolving silver or its insoluble compounds, like the oxide or proteinate, in an excess of some protein and evaporating in vacuo or by electrically or chemically rendering the silver colloidal and stabilizing it with some protein. The result in either case is a material that mixes with water slowly but freely to give dark solutions or mixtures lacking the usual reactions of silver salts. The amount of silver varies enormously, but the properties are very similar. The products may be divided into four types: strong protein combinations; weak protein combinations; stabilized colloidal silver or salts; those electrically prepared.

The **strong silver proteinate** group, which contains 7.5 to 8.5 per cent of metal, is quite irritant and fairly germicidal, being intermediate between the nitrate and the milder forms. It includes protargol, protargentum, and proganol.

The **mild silver proteinate** group, which contains 19 to 25 per cent of metal, is non-irritant and practically not antiseptic. Included are argyrol, argyn, cargentos, solargentum, etc.

The third group includes **collargol,** which is presumed to consist of colloidal silver, formed by reduction with chemicals and made stable by the addition of egg albumin and products of oxidation. It is different from argyrol and protargol in degree rather than in principle, since it contains about 80 per cent of silver. the remainder being protein.

The fourth group is made by forming an arc between two silver electrodes under water. The resulting colloidal solution of the metal is very dilute and unstable and generally of little value.

Theoretically, the protein combinations should correspond to the action of silver proteinates formed with tissue protoplasm. Silver salts give an irritant and germicidal action by precipitating the proteins to form more or less indefinite compounds, which then partially dissolve in excess protoplasm. The solutions so formed can circulate to some extent and are presumed to be mildly antiseptic but not irritating or astringent. Their only *value* must, therefore, rest in *antisepsis.* Since they are quite concentrated and can circulate more or less freely, since the particles of commercial preparations are smaller and seemingly more reactive, because they are non-irritant and there is a tendency to apply them more freely for this reason, they should possess considerable advantage over silver nitrate, provided they are antiseptic. The results of tests to settle the latter point are inconclusive. Some investigators have asserted that antiseptic power is inextricably bound up with irritation and that the more irritant a silver salt is the more antiseptic it will be. Whether this is true or not, the antiseptic power certainly is not high, and much of the benefit attributed to these combinations must be hypothetical or due to demulcent action.

The colloidal silver compounds are *used* mainly on mucous membranes of the eye, urethra, bladder, uterus, vagina, rectum, nose, throat, etc., protargin strong in 0.1 to 10 per cent, protargin mild in 0.1 to 50 per cent concentration. Collargol has been used mainly for intravenous or intramuscular injection in a variety of local infections, which may be benefited by the foreign protein but probably not by the silver. One important use of the first two classes is in the treatment of gonorrhea or as prophylactic in this disease. The preparation is injected into the urethra and held there for a few minutes, then replaced by calomel ointment for 5 minutes. To be efficacious treatment should be given within 3 hours after exposure; after 5 hours it is useless.

Acute poisoning by silver compounds follows the course of any alimentary irritant, causing nausea, abdominal pain, diarrhea, and collapse. The fatal dose, with appropriate treatment, may be very high. Sodium chloride may be given as an antidote, and the remaining measures will be as for any corrosive.

Gold is *less poisonous* than many of the other metals, for it can be fed daily to animals for months without any apparent untoward effects. Large doses by mouth usually cause prompt emesis. Subcutaneously, gold gives paralysis of the central nervous system, with no apparent action on the heart and muscles. It tends to accumulate in the spleen from where it is slowly excreted by the urine and feces.

The only proved value for compounds of this metal is in lupus erythematosus, a chronic skin disease. Either one of the two preparations listed, or possibly some other compounds of gold, is injected intravenously at weekly intervals, the dose being increased gradually from the beginning 5 milligrams up to 75 milligrams for adults. While the treatment is not ideal, because recurrences are common, yet cures are often accomplished, and gold is probably as valuable in this disease as any other drug. Untoward reactions are of frequent occurrence, even causing death, so that much caution must be exercised at all times, and withdrawal of the drug is indicated at the first sign of intolerance. The usual reactions are vomiting, diarrhea, albuminuria, stomatitis, various skin eruptions, and prostration.

The suggestion was made several years ago that the thiosulfate (sanocrysin) was a remedy for pulmonary tuberculosis, and many clinical tests have been given to the proposal. Although the method has not been abandoned, it seems certain that the majority of competent authorities believe gold to be ineffective for this purpose.

Gold salts have also been used more recently in arthritis, rheumatism, psoriasis, leprosy, syphilis, whooping cough, etc.

Platinum has been employed in syphilis but is now considered useless. Uranium nitrate has been applied locally as an antiseptic but is very dangerous.

3. Iodine

Iodine, U.S.P., B.P. Dose: 0.01 Gm., 1/6 grain, U.S.P.; maximum 1/2 grain.

Compound Solution of Iodine (Lugol's Solution), U.S.P. Dose: 0.2 cc., 3 minims, U.S.P.; maximum 10 minims.

Tincture of Iodine, U.S.P. Dose: 0.1 cc., 1½ minims, U.S.P.; maximum 5 minims.

Strong Solution of Iodine, B.P.
Mild Tincture of Iodine, U.S.P. (Weak Solution of Iodine, B.P.)
Stronger Tincture of Iodine (Churchill's Tincture of Iodine), N.F.
Iodine Ointment, U.S.P.
Stainless Iodized Ointment (Unguentum Iodi Denigrescens), N.F.
Ampuls of Iodine (Iodine Swabs), N.F.
Iodine Petroxolin, N.F.
Iocamfen, N.R.
Camiofen Ointment, N.R.
Glycerite of Iodine and Zinc Iodide, N.F.

Iodine stains the skin and other tissues brown, producing some *irritation and inflammation*, which may be increased to vesication and corrosion by repeated application. It is absorbed readily from any surface but is quickly converted to iodides, so that no poisoning results except from large concentrations. When sufficient amounts are swallowed, there are vomiting, abdominal pain, and purging; and hypodermic injection produces renal congestion, pulmonary hemorrhage, depressed circulation, and collapse.

Iodine is *employed* as an antiseptic on wounds, before operation, in various infections of mucous membranes of the throat, urethra, uterus, etc., and injected into cysts and cavities; it is capable of excellent results under these conditions if the bacteria are not too deeply imbedded. The various commercial preparations possess no advantage over the official tincture, which is the agent of choice, and the so-called colorless or stainless mixtures are valueless for applying iodine because they contain none of the element. Iodine is fairly efficient against such skin diseases as ringworm, lupus, and pityriasis. Injected into the site of a snake bite, it may by oxidation destroy the venom. It is also considered a temporary chemical antidote for strychnine in the alimentary tract, although there are probably better reagents for this purpose.

Iodine is painted on the skin as a *counter-irritant* in a variety of afflictions, where it is presumed to act by allaying inflammation, by promoting the absorption of exudates, and by reducing pain. Thus, pleurisy, rheumatism, phlebitis, erysipelas, etc., are treated in this manner. Iodine cannot be considered specific but merely has the action of other counter-irritants in mild form. The internal use of iodine, like the iodides in exophthalmic goiter, will be discussed later.

Poisonous doses give rise to the usual symptoms of gastroenteritis, 2 to 3 grams being usually considered fatal, although recovery has taken place after 10 grams. The treatment would consist in evacuation and in the administration of sodium thiosulphate as antidote or of alkalies and of demulcents.

4. Chlorine and Bromine

Solution of Sodium Hypochlorite (Labarraque's Solution), U.S.P., B.P. An aqueous solution of chlorine compounds of sodium, equivalent to not less than 2.5 per cent of available chlorine.

Diluted Solution of Sodium Hypochlorite (Modified Dakin's Solution), U.S.P., B.P.

Antiformin, N.R. A strongly alkaline solution of chlorinated soda.

Hychlorite, N.R. 3.85 per cent of available chlorine.

Chlorinated Lime (Calx Chlorinata, Chloride of Lime, Bleaching Powder), B.P. A product resulting from the action of chlorine upon calcium hydroxide and yields not less than 30 per cent of available chlorine.

death, so that much caution must be exercised at all times, and withdrawal of the drug is indicated at the first sign of intolerance. The usual reactions are vomiting, diarrhea, albuminuria, stomatitis, various skin eruptions, and prostration.

The suggestion was made several years ago that the thiosulfate (sanocrysin) was a remedy for pulmonary tuberculosis, and many clinical tests have been given to the proposal. Although the method has not been abandoned, it seems certain that the majority of competent authorities believe gold to be ineffective for this purpose.

Gold salts have also been used more recently in arthritis, rheumatism, psoriasis, leprosy, syphilis, whooping cough, etc.

Platinum has been employed in syphilis but is now considered useless. Uranium nitrate has been applied locally as an antiseptic but is very dangerous.

3. Iodine

Iodine, U.S.P., B.P. Dose: 0.01 Gm., 1/6 grain, U.S.P.; maximum 1/2 grain.

Compound Solution of Iodine (Lugol's Solution), U.S.P. Dose: 0.2 cc., 3 minims, U.S.P.; maximum 10 minims.

Tincture of Iodine, U.S.P. Dose: 0.1 cc., 1½ minims, U.S.P.; maximum 5 minims.

Strong Solution of Iodine, B.P.
Mild Tincture of Iodine, U.S.P. (Weak Solution of Iodine, B.P.)
Stronger Tincture of Iodine (Churchill's Tincture of Iodine), N.F.
Iodine Ointment, U.S.P.
Stainless Iodized Ointment (Unguentum Iodi Denigrescens), N.F.
Ampuls of Iodine (Iodine Swabs), N.F.
Iodine Petroxolin, N.F.
Iocamfen, N.R.
Camiofen Ointment, N.R.
Glycerite of Iodine and Zinc Iodide, N.F.

Iodine stains the skin and other tissues brown, producing some *irritation and inflammation,* which may be increased to vesication and corrosion by repeated application. It is absorbed readily from any surface but is quickly converted to iodides, so that no poisoning results except from large concentrations. When sufficient amounts are swallowed, there are vomiting, abdominal pain, and purging; and hypodermic injection produces renal congestion, pulmonary hemorrhage, depressed circulation, and collapse.

Iodine is *employed* as an antiseptic on wounds, before operation, in various infections of mucous membranes of the throat, urethra, uterus, etc., and injected into cysts and cavities; it is capable of excellent results under these conditions if the bacteria are not too deeply imbedded. The various commercial preparations possess no advantage over the official tincture, which is the agent of choice, and the so-called colorless or stainless mixtures are valueless for applying iodine because they contain none of the element. Iodine is fairly efficient against such skin diseases as ringworm, lupus, and pityriasis. Injected into the site of a snake bite, it may by oxidation destroy the venom. It is also considered a temporary chemical antidote for strychnine in the alimentary tract, although there are probably better reagents for this purpose.

Iodine is painted on the skin as a *counter-irritant* in a variety of afflictions, where it is presumed to act by allaying inflammation, by promoting the absorption of exudates, and by reducing pain. Thus, pleurisy, rheumatism, phlebitis, erysipelas, etc., are treated in this manner. Iodine cannot be considered specific but merely has the action of other counter-irritants in mild form. The internal use of iodine, like the iodides in exophthalmic goiter, will be discussed later.

Poisonous doses give rise to the usual symptoms of gastroenteritis, 2 to 3 grams being usually considered fatal, although recovery has taken place after 10 grams. The treatment would consist in evacuation and in the administration of sodium thiosulphate as antidote or of alkalies and of demulcents.

4. Chlorine and Bromine

Solution of Sodium Hypochlorite (Labarraque's Solution), U.S.P., B.P. An aqueous solution of chlorine compounds of sodium, equivalent to not less than 2.5 per cent of available chlorine.

Diluted Solution of Sodium Hypochlorite (Modified Dakin's Solution), U.S.P., B.P.

Antiformin, N.R. A strongly alkaline solution of chlorinated soda.

Hychlorite, N.R. 3.85 per cent of available chlorine.

Chlorinated Lime (Calx Chlorinata, Chloride of Lime, Bleaching Powder), B.P. A product resulting from the action of chlorine upon calcium hydroxide and yields not less than 30 per cent of available chlorine.

Chloramine-T (Chlorazene, Tolamine), U.S.P., N.R., B.P. Sodium para toluenesulfonchloramide, $CH_3\cdot C_6H_4\cdot SO_2NaNCl\cdot 3H_2O$, 1:4.

Dichloramine-T, U.S.P., N.R. Paratoluenesulfondichloramide, $CH_3\cdot C_6H_4SO_2NCl_2$, 1:4.

Chlorinated Paraffin (Chlorcosane), U.S.P., N.R.

Halozone, N.R. Parasulfondichloramidobenzoic acid, $HOOC\cdot C_6H_4\cdot SO_2NCl_2$, 1:4.

Azochloramid, N.R. N,N-dichlorazo dicarbonamidine, $NH_2(ClN:)CN:NC\ (ClN)NH_2$.

Dibromin, N.R. Dibrombarbituric acid.

Chlorine combines with most other elements, destroys organic compounds, and liberates available oxygen from water. It is, therefore, a strong poison to protoplasm and an excellent *antiseptic*. It is somewhat irritating to the skin and very much so to mucous membranes, especially to those of the respiratory tract. Inhalation of chlorine may cause severe poisoning and even death by local action. The gas quickly reacts with tissue compounds, and free chlorine is thus not absorbed, except in small quantities. The destructive action on colors and other organic materials is a serious disdavantage to the use of the gas for disinfecting rooms and fabrics.

Bleaching powder, on account of its alkalinity, is very irritant and seldom applied as a body antiseptic, except for the intact skin. It is one of the cheapest and best germicides for excrements, refuse, latrines, etc., and in the proportion of ½ teaspoonful to 1 gallon is an excellent sterilizing agent for temporary drinking water. It is also injected into the site of a snake bite as an antidote.

Chlorine itself is universally employed to disinfect drinking water. The gas was once thought to be a prophylactic and cure for infectious diseases of the upper respiratory passages (colds, etc.), but this has been discredited. **Chlorinated soda solution** is more stable and convenient for local application. The latter has been employed extensively for a very long time, but experience during the World War paved the way for great improvements in preparation and application. The surgical solution now used differs from the former ones in containing less hypochlorite and in being very slightly alkaline. It is not greatly irritating and can be used to irrigate wounds, in which the dead tissue is dissolved and healing is promoted. The solvent action softens gut and destroys silk ligatures, which indicates caution to avoid loss of stitches. The strongly alkaline solutions are limited to skin diseases, to the disinfection of fabrics and glassware, and to treatment of fungus growths like ringworm of the feet.

The action of chlorine on protein is said to form **chloramines,** which have notable antiseptic power. Several such compounds have been introduced to replace the less convenient chlorinated soda solution. Chloramine, a soluble, relatively stable substance, is presumed to be three or four times as strong and less irritant but lacks any solvent properties. It is used in wounds (1 to 2 per cent), in the eye, nose, throat, urethra, bladder, and uterus (0.1 to 1 per cent). Dichloramine is a stronger, insoluble compound, which is more solvent but also more irritating than chloramine. It is employed, dissolved in chlorinated paraffin to give a relatively unstable solution, for a gradual, sustained action as a nasal spray (2 per cent); as an application to wounds (5 per cent); and in eye infections (0.5 per cent). It is said to prevent epithelial growth and thus retard healing. Both the compound and its solution are decomposed by sunlight.

Halozone is used as a convenient agent to sterilize drinking water, because it is powerfully disinfectant and practically tasteless. A tablet containing 0.004 gram is added to a quart of water for extemporaneous use.

Azochloramid is employed in buffered solution (1:1600 to 1:3300) or in glyceryl triacetate (1:500) in the same way as sodium hypochlorite.

Bromine is intensely corrosive to the skin and mucous membranes, much more so than other caustics, a few seconds' exposure forming wounds which are very slow to heal. Dilute solutions of bromine and dibromin have been used rarely as antiseptics.

5. Manganese

Potassium Permanganate, U.S.P., B.P. $KMnO_4$. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Tablets of Potassium Permanganate, N.F.

Zinc Permanganate, N.R. $Zn(MnO_4)_2 \cdot 6H_2O$.

Soluble Manganese Citrate (Manganese and Sodium Citrate), N.F.

Manganese is very *widely distributed* in the vegetable and animal kingdoms, being a constant component of the ash of many plants and in greater or lesser amounts in practically all animal organs. The quantity in the blood of man is not over 0.05 gram per liter. It is undoubtedly an essential element, being in some way necessary in reproduction.

The ordinary salts administered by the mouth have no noticeable effect, because the metal is absorbed to but a very slight degree and is stored and excreted slowly. Injected hypodermically it causes more or less severe poisoning. Inflammation of the kidneys and intestines during excretion, fatty degeneration of the liver, epileptic convulsions, fall of blood pressure, and respiratory paralysis are the most important symptoms. Potassium permanganate causes some irritation upon mucous membranes, and large amounts are even corrosive in the alimentary tract. It is quickly reduced by any organic matter, giving a rapid but short period of caustic action, also a powerful *germicidal action* for the same reason. The quick reduction makes the latter only superficial.

The permanganates are *applied* to wounds, burns, in the urethra, on the feet and hands, in concentrations of 1:5000 to 1:100, to secure disinfection, deodorizing, and hemostatic effects. They are employed as *antidotes* for hydrocyanic acid, phosphorus, and morphine in the intestinal tract but never after absorption. The hypodermic injection of potassium permanganate has been recommended for morphine, but it is difficult to see how this could be of any value. It is also injected around a recent snake bite to oxidize the toxin and rubbed into the skin in rhus poisoning for the same purpose. As an antidote for strychnine and for phenol, it is of doubtful value.

Manganese dioxide and potassium permanganate have been recommended and used as *emmenagogues* and as *hematinics* in anemia. Since there is little or no absorption of either, it is hard to imagine an action on the uterus, and the clinical evidence for efficacy in anemia is very poor.

6. Peroxides

Solution of Hydrogen Peroxide (Hydrogen Dioxide, Peroxide), U.S.P., B.P. An aqueous solution containing about 3 per cent by weight of H_2O_2. Dose: 4 cc., 1 fluidrachm, U.S.P.

Calcium Peroxide, N.R. 60 per cent of CaO_2 equal to 13.3 per cent of available oxygen. Dose: 0.06 to 0.3 Gm.

Sodium Peroxide (Oxone), N.R. 90 per cent of Na_2O_2 equal to 18.4 per cent of available oxygen.

Hydrogen peroxide decomposes quickly in contact with a variety of substances, including finely divided metals or oxides, pus, ferments, blood, yeasts, and other organic matter. The nascent oxygen liberated is a powerful *bactericide*, being the equal of mercuric chloride, but its action lasts only as long as the gas is liberated; it will destroy typhoid bacilli in a few minutes. Other organic materials, including colors, are also oxidized without selection, so that the efficacy is soon lost. Hydrogen peroxide is a harmless substance, except in concentration or when the resulting gas is confined, as in cavities or in the blood, where gas emboli may be produced and cause sudden death. The 30 per cent solution (**perhydrol**) is said to be caustic, forming a white eschar. Hydrogen peroxide can be easily absorbed, but its decomposition is so rapid in the presence of tissue that its journey is not extensive, notwithstanding the claims that it has been found in the urine after hypodermic injection. The gas foam formed during decomposition aids mechanically in carrying away old debris and in cleansing wounds.

Hydrogen peroxide is *used* for irrigating and disinfecting wounds, ulcers, gonorrheal infections, for skin diseases, and as a mouth wash. It is an excellent sterilizer for water, provided too much organic matter is not present. Because of the oxygen evolved, it is used as an antidote for poisoning by hydrocyanic acid, for bleaching hair and fabrics, and as a preservative for liquids. A small amount will effectually destroy or inhibit the bacteria in milk, but the ferments and possibly the vitamins are also affected. A **solid peroxide**, containing 35 to 40 per cent of absolute hydrogen peroxide with urea, carbamates, etc., was introduced with the idea of slower decomposition but has never become popular.

The **metal peroxides** are readily decomposed by acids, less so by water, with the formation of nascent oxygen, in all cases more gradually than the hydrogen compound. They differ among themselves only in solubility, alkalinity, and the action of the metallic ion. They are used in the same way as hydrogen peroxide to sterilize water; for skin diseases with tartaric acid and potassium iodide; as gastric and intestinal antiseptics; and in other conditions. The sodium compound is a convenient source of extemporaneous oxygen. Its alkalinity limits any extensive employment in therapy, but it is used in some skin diseases and as a purifier of air, where the alkalinity is claimed to absorb carbonic acid, while the nascent oxygen sterilizes. Zinc peroxide has been added to dusting powders and ointments, while the magnesium compound is an ingredient of tooth powders.

The **organic peroxides** are strongly recommended as germicides, but they are very unstable and inconvenient to handle, since care must be exercised to prevent explosions. Acetozone and alphozone were formerly used somewhat, and benzoyl peroxide is applied to the treatment of burns and of poisoning by species of *Rhus.*

7. Phenol

Phenol (Carbolic Acid), U.S.P., B.P. C_6H_5OH. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Liquefied Phenol (Liquefied Carbolic Acid), U.S.P., B.P. Dose: 0.06 cc., 1 minim, U.S.P.; maximum 3 minims.

Phenolated Water (Carbolic Acid Water), N.F.

Phenol Ointment, U.S.P., B.P.

Glycerite of Phenol (Glycerin of Phenol), N.F., B.P.

Phenol Lozenge (Trochiscus Acidi Carbolici), B.P.

Phenol Suppositories, B.P.

Toothache Drops (Odontalgicum), N.F.

Phenolated Oil (Carbolized Oil), N.F.

Camphorated Phenol, N.F.

Phenolated Solution of Iodine (French Mixture, Boulton's Solution), N.F.

Compound Solution of Sodium Borate (Dobell's Solution), N.F.

Aromatic Spray (Aromatol), N.F.

Phenol, in dilute solution, checks the growth and reproduction of bacteria, protozoa, plant cells, spermatozoa, and cells of higher animals and prevents the action of some enzymes. Very dilute solutions, however, stimulate growth and action. Concentrated phenol *kills* practically *all living tissue,* but this is not equal for various organisms. The spores of anthrax are killed only after 2 or 3 days in a 5 per cent solution and are not destroyed even after 15 days in a more dilute solution. The bacillus itself is quickly rendered inert in a 0.5 per cent solution, while the tubercle organism requires 24 hours in ten times that strength. Emulsin, diastase, and myrosin are not much affected, but pepsin, ptyalin, and rennin are weakened by the presence of 5 per cent.

Protein, in solution or cell, is precipitated in very loose chemical combination, from which the phenol may be washed out easily. The action is, therefore, not limited but penetrates to the deeper layers of cells. Concentrated preparations *applied to the skin* cause a brief period of pain, with subsequent loss of sensation, which may be almost complete anesthesia and which penetrates through the corium. There is formed a white crust, later turning red and falling off, leaving a yellowish, pigmented spot for some time. Dilute solutions give a tanned appearance to the skin with tingling and burning, followed often by opacity and contraction of the epidermis and a sense of numbness. If evaporation is prevented and contact continued for some time, a dry gangrene may be caused during the penetration.

On wounds or *mucous membranes*, the preliminary irritation and amount of corrosion are increasingly severe, but the later loss of feeling is more complete. If the phenol is in sufficient concentration, sloughing and acute inflammation may follow a primary white precipitate of coagulated albumin. If the drug is swallowed, the results are similar to those from other corrosives like the mineral acids; death may occur from shock in a very short time.

Phenol is *absorbed* readily from most surfaces, but this later becomes very slow. One-third to one-half is burned completely. The remainder is partly oxidized to hydroquinone and pyrocatechin and *excreted* in the urine in combination with glucuronic acid or sulfuric acid. The compounds are previously or later oxidized to green or brown products which give a smoky or dark color to the urine.

The *systemic action* of phenol is not very well understood. In man it probably consists in primary stimulation and subsequent paralysis of the entire central nervous system; the respiratory, circulatory, vomiting, and secretion centers appear to be thus affected. In animals spinal convulsions seem to be the rule, but these are not observed in man. Death occurs from failure of the respiration. Direct contact paralyzes muscles, and the same effect apparently occurs in the heart muscle after absorption.

Large doses may cause immediate coma and death, but more gradual poisoning (1 to 10 grams) gives a series of symptoms. These are salivation, drowsiness, giddiness, depression and languor, sometimes delirium, headache, nausea and vomiting, noise in the ears and deafness, pallor, irregular pulse and respiration, cold perspiration, collapse, unconsciousness, and asphyxia. The temperature may be higher but usually drops. Autopsy shows inflammation of the gastro-intestinal tract and frequently fatty degeneration of the liver and kidneys. The lethal dose is generally 8 to 10 grams but may vary greatly under prompt treatment. Children are very susceptible.

No method of *treatment* probably will be adequate if coma has already started. If the poisoning has been caused from local use, the phenol should be washed out with diluted alcohol, and an oil dressing applied. If from oral ingestion, the stomach must be washed out with dilute alcohol to remove the unabsorbed drug, vinegar being sometimes used as a substitute for the alcohol. Various antidotes for phenol have been recommended, such as syrup of lime, potassium permanganate, alcohol, sulfates, saline intravenously, etc., probably none effective. It has been shown that alcohol is not only inadequate but even aids the absorption, if not immediately removed. Sulfates do not combine with phenol, as has been supposed, but they are harmless, and some of them may aid by purgative action. Syrup of lime is presumed to form an insoluble phenate.

Carbolic acid is of interest as an *antiseptic* because it was the first of this class, but its use is now much less prevalent, because more efficient and less dangerous remedies have been introduced. It is still used to some extent in ½ to 5 per cent solution as an application to wounds and infections; also, to disinfect or prevent growth of germs in rooms, on the hands, instruments, linen, excreta, etc. For the latter one of the impure mixtures (tar) is more economical. Oils or fats render it entirely ineffective, while salts increase the germicidal power by salting out. Phenolized oil is useless because bacteria retain their activity in it even after 3 months. Dilute solutions in dressings or bandages are liable to cause a dry gangrene, which may endanger life or necessitate amputation. Phenol has been injected locally for tubercular bones and joints. The vapor is inhaled for putrid bronchitis and pulmonary gangrene, but it has been shown that the vapor of phenol is almost without effect on bacteria. At one time the drug was given by mouth as an intestinal antiseptic, a use that is almost abandoned because the efficiency is not high, and the danger of poisoning is great. **Sodium phenolsulfonate** is much less toxic but inadequate for this purpose, although it has been employed in fermentation and in typhoid fever.

Phenol has had considerable popularity as an *antiparasitic* for scabies, head lice, etc., but it is usually now considered inadvisable. Occasionally, the undiluted drug is applied to cauterize wounds, bites, and ulcers and as a sclerosing agent, the loss of sensation caused by its local action being of some advantage. This *anesthesia* can be utilized also for itching, burns, toothache (in a cavity), earache, and even minor operations.

The *systemic action* has suggested trials in convulsive diseases like tetanus, in which it is injected intravenously or intrathecally, with or without antitoxin. By some it is claimed to be almost specific.

8. Picric Acid

Trinitrophenol (Picric Acid), U.S.P., B.P. $C_6H_2(OH)(NO_2)_3$ 1:2:4:6.

Picric acid is *used* as a dressing for burns, and sometimes for wounds and eruptions, in the form of a saturated aqueous solution, which exerts antiseptic, protective, local anesthetic, local stimulant, and astringent effects. It should not be applied over a large surface, nor should the stronger alcoholic solution be used, because dangerous poisoning might result. As with phenol, ointments are illogical.

The compound is readily absorbed from all surfaces and excreted in the urine, mostly unchanged but partially as **picramic acid.** Orally, 1 to 2 grains may produce severe *poisoning* but with favorable prognosis due to rapid excretion. Gastroenteritis, nephritis, and hepatitis are produced by a destructive action upon the red blood-corpuscles, and violent convulsions are sometimes observed. Workers in factories are frequently afflicted with eczematous rashes. Stains on clothing may be removed by magnesium or calcium carbonate or by potassium sulphate and subsequent washing with soap.

Other nitrophenols give similar poisoning, but nitrobenzene causes toxic effects like those from aniline. Occasional use of the latter as a flavoring agent should be condemned.

Most of the nitrophenols stimulate the metabolism in a way which would indicate an action through the thyroid gland. Dinitrophenol (2,4) and others have been administered to reduce weight in obesity. The results were highly encouraging at first, but the method is now known to be unpredictably dangerous. Skin rashes, liver injury, deafness, agranulocytosis, peripheral neuritis, cataract, etc., have been reported as caused by dinitrophenol, sometimes even with just a few doses; and there have been several deaths.

9. Cresol

Cresol, U.S.P., B.P. A mixture of isomeric cresols, $CH_3{\cdot}C_6H_4OH$, obtained from coal tar. Dose: 0.06 cc., 1 minim, U.S.P.; maximum 3 minims.

Saponated Solution of Cresol (Compound Cresol Solution, Liquor Cresolis Compositus), U.S.P., B.P.

Cresatin, N.R. Metacresyl Acetate, $CH_3{\cdot}C_6H_4{\cdot}OCOCH_3$ 1:3.

The cresols and higher homologues of phenol are very similar to the latter. The meta derivative of cresol is presumed to be less toxic and irritant and more antiseptic, while the ortho and para forms are more poisonous. The differences, however, are too small to be practical, and the *germicidal action* may be presumed to be but little more than that of phenol. The toxicity may be less because of greater dilution, but the cresols are far from being non-poisonous. They are absorbed in the same way and give rise to lesions and systemic symptoms exactly as does phenol.

The cresols, being little soluble in water, are usually made into an emulsion with soaps. These have the advantage of penetrating bacteria, because of their insolubility in the medium, but possess the disadvantage of disagreeable odor and variability of composition. The solutions are *applied in surgery,* gargles, irrigations, and wet dressings in about 0.25 to 1 per cent solutions or for clothing, excrement, or instruments in 2 to 5 per cent solution. Although they have the same drawbacks as does phenol, it has been suggested that they be used as intestinal antiseptics. A dusting powder containing 3 per cent of tricresol has been used for body lice. Added to serums in the proportion of 0.5 per cent, cresols preserve the serum and act as local anesthetic during injection. Higher concentrations in solutions designed for intraspinal injection have caused serious collapse.

There should be mentioned at this point the numerous *commercial preparations,* which have approximately the composition and properties of cresol solution. Lysol, lysitol, lysosolveol, sapokresol, phenolin, solveol, solutol, kresin, creolin, sagrotan, saprol, and cresolin are but a few of the preparations belonging to this class.

Triorthocresyl phosphate, as an adulterant of ginger preparations, was the responsible agent in the so-called "jake poisonings" a few years ago.

10. Creosote and Guaiacol

Creosote, U.S.P., B.P. A mixture of phenols, obtained from wood tar. Dose: 0.25 cc., 4 minims, U.S.P.; maximum 8 minims.

Creosote Carbonate (Creosotal), U.S.P., N.R. Dose: 1 Gm., 15 grains, U.S.P.

Guaiacol, U.S.P., B.P. $CH_3O{\cdot}C_6H_4OH$. Dose: 0.5 cc., 8 minims, U.S.P.; maximum 10 minims.

Guaiacol Carbonate (Duotal), U.S.P. Dose: 1 Gm., 15 grains.

Guaiacol Benzoate (Benzosol), N.R. Dose: 0.2 to 0.6 Gm.

Calcium Creosotate (Calcreose), U.S.P. *A mixture of the calcium compounds of the constituents of creosote.* Dose: 0.5 Gm., 8 grains.

Potassium Guaiacolsulfonate (Thiocol), N.F. $C_6H_3{\cdot}OH{\cdot}OCH_3{\cdot}SO_3K$. Dose: 0.5 Gm., 8 grains for humans or swine.

Syrup of Potassium Guaiacolsulfonate, N.F. Dose: 4 cc., 1 fluidrachm.

Phenoco, N.R. A mixture of coal-tar creosote and higher phenol homologues in soap solution.

Proposote, N.R. Creosote phenylpropionate. Dose: 0.6 cc. in capsule.

Creosote is wood tar from which the more volatile components have been removed and consists of about 60 per cent of guaiacol and smaller quantities of the homologous creosols. The *action* of creosote or guaiacol is thus approximately the same and similar to that of phenol. They are much less irritating and toxic and probably more antiseptic and antipyretic. They are also less convulsive in animals and give more cardiac depression, sometimes causing dangerous collapse. Otherwise the effects are like those from phenol. Administered by mouth for long periods, there may be disagreeable disturbances of digestion, which can be obviated by using insoluble esters. These are but slowly hydrolyzed in the intestines and excreted largely unchanged in the feces. The carbonates represent all the advantages of this class and, being the cheapest, are usually preferred. Beside the derivatives of guaiacol already listed, the cinnamate (styracol), the salicylate (guaiacol salol), methyl guaiacol (veratrol), methyl glycoguaiacol (monotal), the glycerin derivative (guaiamar), the chloride of diethyl glycocollguaiacol (guaiasanol) are sometimes used.

Creosote and guaiacol are *employed* as antiseptics in much the same way as phenol, but their main value in medicine has usually been considered to be in tuberculosis and chronic bronchitis, where they are administered three times a day after meals, the dose being gradually increased to 10 drops or more. If they are not tolerated in this way, the carbonates may be substituted. Inhalation, rectal injection, and other methods have been tried without any apparent advantage over the oral route. Medical opinion has been much divided over the question of efficacy. It is generally claimed by some that the appetite, metabolism, and weight are increased and that the fever, night-sweats, and cough are lessened, but it is doubtful if the ultimate effect upon the disease is any better than is now gained by hygienic measures without drugs. Creosote certainly has no influence upon the bacillus but may exert a favorable effect on the symptoms by antipyretic, expectorant, and stomachic action. The increase in bronchial secretion may be of value in bronchitis.

As *intestinal antiseptics,* these drugs are of doubtful efficiency, although probably as much so as any of the other drugs used for this purpose. Creosote water is frequently administered to check fermentations in the stomach. Guaiacol carbonate is non-toxic and probably as useless. Guaiacol (20 to 30 drops) is sometimes rubbed into the dry skin of the abdomen to reduce body temperature. This causes considerable diaphoresis. The local anesthetic properties may be used in itching skin diseases and in dentistry. Creosote has been used as an antiparasitic for body lice in the same way as phenol and cresol. Rubbed into the chest, it is presumed to hasten the absorption of exudates in pleurisy.

11. Resorcinol

Resorcinol (Resorcin), U.S.P., B.P. $C_6H_4(OH)_2$ 1:3. Dose: 0.125 Gm., 2 grains, U.S.P.; maximum 10 grains.

Compound Ointment of Resorcinol, N.F.

Strong Paste of Resorcinol (Lassar's Stronger Resorcinol Paste), N.F.

Mild Paste of Resorcinol (Lassar's Mild Resorcinol Paste), N.F.

Resorcinol Monacetate (Euresol), N.R. $CH_3 \cdot COO \cdot C_6H_4OH$ 1:3.

The dihydroxybenzenes are all *reducing agents*, especially in alkaline solution, and hence poisonous, resorcinol less than hydroquinone and pyrocatechin. Dilute solutions coagulate albumin, and stronger ones cauterize, although not to the same extent as phenol. The absorption, excretion, and action are similar to those of the latter but in milder degree. In man, convulsions have been observed. Resorcinol is absorbed readily and excreted in the urine combined with glucuronic acid.

Resorcinol is *used* as an antiseptic under the same conditions as phenol. For the urethra, ½ to 2 per cent solutions are injected, which may cause some irritation and pain. The internal use of resorcinol is not to be recommended, although a teaspoonful of ½ to 1 per cent solution has been prescribed in various conditions, notably gastric fermentation and summer diarrhea. As an antiparasitic and caustic in skin diseases, it may be used in 5 to 50 per cent ointment or in 10 to 20 per cent glycerin solution. Weaker aqueous solutions (2 to 6 per cent) are recommended for the scalp to remove dandruff. It has been recommended and used as an antipyretic, but its action is too brief, and serious collapse, with delirium, intoxication, and twitching, has been observed all too frequently.

Hexylresorcinol (Caprokol, S.T. 37) is sometimes used for urinary antisepsis. It is claimed to be much more germicidal than phenol and relatively non-toxic, for 1 to 7 grams has been given to adults with no apparent ill effect. Normal urine containing 1 part in 10,000 has been found to be inimical to certain types of bacteria and less so to others. It is also employed as anthelmintic for all kinds of worms, especially ascarides, for which some claim it is the best of all drugs. The preparations of hexylresorcinol were omitted recently from New and Nonofficial Remedies on technical grounds, chiefly because the manufacturer refused to give up the designation S.T. 37.

12. Thymol

Thymol, U.S.P., B.P. A phenol, $CH_3{\cdot}C_6H_3(OH)(C_3H_7)$ 1:3:4. Dose: antiseptic 0.125 Gm., 2 grains, anthelmintic divided into three doses 2 Gm., 30 grains, U.S.P.; maximum 30 grains.

Thyme, N.F. The dried leaves and flowering tops of *Thymus vulgaris* (*Labiatæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Thyme, N.F. Dose: 4 cc., 1 fluidrachm.

Oil of Thyme, N.F. Dose: 0.1 cc., 1½ minims.

Syrup of Thyme, N.F. Dose: 4 cc., 1 fluidrachm.

Antiseptic Solution (Liquor Antisepticus), N.F.

Alkaline Aromatic Solution, N.F.

Thymol Iodide (Aristol), U.S.P., N.R. A mixture of iodine derivatives of thymol, principally dithymol-diiodide, $(CH_3{\cdot}C_6H_2{\cdot}C_3H_7{\cdot}OI)_2$.

Chlorthymol (Monochlorthymol), N.F. $C_6H_2{\cdot}CH_3{\cdot}OH{\cdot}C_3H_7{\cdot}Cl$ 1:3:4:6.

Thymol has but slight local *action* and is very slowly but completely absorbed, so that it is much less poisonous than phenol. Even after absorption its toxicity is not great, there being but a temporary depression of the nervous system, with no convulsions. The urine is darkened as with phenol.

Because of insolubility, its antiseptic worth under the usual conditions is very small, but it is *used* as an agreeable gargle and mouth wash. It is also employed to wash out cavities and as lotion for wounds and ulcers, the antiseptic efficiency being somewhat greater than equally concentrated phenol, although not actively germicidal. As an antipyretic, thymol is quite inferior. It is given as an intestinal antiseptic and is probably for this purpose as valuable as any of the phenols, because of its poor absorption. One of the chief uses for thymol has been in *hookworm,* in which it is given in large doses, the simultaneous administration of fats or oils being avoided. Recently carbon tetrachloride has almost entirely replaced it.

Thymol iodide is one of the numerous substitutes for iodoform as a dusting powder for wounds, ulcers, etc. It is as efficient as any but, like the rest, inferior to iodoform.

Chlorthymol, which is more soluble than thymol, is used locally in the same way.

13. Benzoates

Benzoic Acid, U.S.P., B.P. $C_6H_5 \cdot COOH$. Dose: 1 Gm., 15 grains, U.S.P.

Compound Ointment of Benzoic Acid, N.F.

Ammonium Benzoate, U.S.P., B.P. $NH_4C_7H_5O_2$. Dose: 1 Gm., 15 grains, U.S.P.

Sodium Benzoate, U.S.P., B.P. $NaC_7H_5O_2$. Dose: 1 Gm., 15 grains, U.S.P.

Benzoin, U.S.P., B.P. The balsamic resin obtained from *Styrax Benzoin,* known in commerce as Sumatra Benzoin, or from *S. tonkinensis* or from other species of *Styrax,* known in commerce as Siam Benzoin (*Styraceæ*). Dose: 1 Gm., 15 grains, U.S.P.

Tincture of Benzoin, U.S.P. Dose: 1 cc., 15 minims.

Compound Tincture of Benzoin (Friar's Balsam, Traumatic Balsam), U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Storax (Styrax, Liquid Storax, Prepared Storax), U.S.P., B.P. A balsam obtained from the trunk of *Liquidambar orientalis,* known in commerce as Levant Storax, or of *L. styraciflua,* known in commerce as American Storax (*Hamamelidaceæ*). Dose: 1 Gm., 15 grains, U.S.P.

Applied in concentrated form, benzoic acid is irritant to all surfaces, in dilution to the mucous membranes and in vapor to the bronchial tissue, increasing secretions. The *antiseptic power* is about the same as that of salicylic acid, but the salts are inferior in this respect to those of the latter. All the preparations are readily absorbed and rapidly excreted as hippuric or benzoic acid in the urine, which is moderately increased, as is also the excretion of nitrogen. The systemic effects seem to be like those of salicylates in a much smaller degree.

The benzoates are administered *by mouth* to bring about intestinal and urinary antisepsis and diuresis and for the treatment of rheumatism, in which they are much less effective than salicylates. They are also commonly employed as food preservatives. Benzoin and storax and their preparations are *applied locally* for antiseptic, local stimulant, and sedative effects on wounds, ulcers, bed-sores, and skin diseases and for the treatment of freckles, sunburn, and chapped hands and lips. Inhalations of vapors from boiling water and the compound tincture orally are considered excellent methods for treating bronchitis, as well as hoarseness, catarrh, sore throat, etc. They are sometimes, also, used as antiparasitics. Ammonium benzoate is claimed to be efficient as a urinary antiseptic, presumably like any acidifier. The sodium salt has recently been administered intravenously for gastro-duodenal ulcers and also for abscesses and gangrene of the lungs.

14. Eucalyptus

Oil of Eucalyptus, U.S.P., B.P. The volatile oil distilled from *Eucalyptus Globulus* (*Myrtaceæ*) and from some other species of *E.* Dose: 0.5 cc., 8 minims, U.S.P.

Eucalyptol (Cineol), U.S.P., B.P. A substance, $C_{10}H_{18}O$, obtained from oil of eucalyptus and from other sources. Dose: 0.3 cc., 5 minims, U.S.P.

Oil of Cajuput (Oil of Cajeput), B.P. The volatile oil distilled from the fresh leaves and twigs of several varieties of *Melaleuca Leucadendron*, especially the var. *Cajeputi* and the var. *minor* (*Myrtaceæ*), rectified by steam distillation.

Spirit of Cajuput, B.P.

Eucalyptus oil and its chief component, cineol, which could advantageously replace it, are similar to other volatile oils. They give mild irritation and some antisepsis. Large doses have caused fatal collapse, and smaller ones may cause skin eruptions, due to idiosyncrasies. They impart a violet odor to the urine, as does turpentine oil.

The oil has been *used* as antiseptic in certain skin diseases and in bronchitis, where it also exerts expectorant action. For the latter purpose, it is administered by mouth or inhalation or in the form of an oil spray, which may be of value also in coryza. As a counter-irritant in rheumatic and other conditions, it is a component of many commercial preparations. All eucalyptus compounds have been recommended in malaria, but they are decidedly inferior to quinine. The extensive popularity at one time was probably due to the fact that eucalyptus trees will reduce the incidence and even drive malaria from infected districts, because of the capacity that they have for taking up water and thus drying up the soil, to prevent mosquito breeding. Eucalyptol is a fairly good insecticide and has been employed as anthelmintic for hookworm, although decidedly inferior to thymol and carbon tetrachloride. The leaves and galenicals are stomachic and carminative but are not often administered.

Cajuput oil, since it contains chiefly cineol, is of value in the same way as the latter. It is sometimes given in hysteria and other nervous affections and is presumed to be an anodyne for toothache.

15. Iodoform

Iodoform, U.S.P., B.P. Triiodomethane, CHI_3.
Iodoform Suppositories, B.P.

Iodoform in itself has no local action and is certainly not antiseptic, but in the presence of serum or mucous membranes changes take place which are not definitely understood. The beneficial *local effect* has been laid to a number of factors, such as slow liberation of iodine, establishment of unfavorable medium for bacterial growth, and the formation of a crust which prevents invasion, but none of these is entirely satisfactory. The drug exerts healing, antiseptic, analgesic, and protective effects on abraded surfaces. It is absorbed from such areas in unknown form and in variable amounts, sometimes sufficient to cause fatal toxicity. The absorption is equally erratic from mucous membranes. Excretion takes place very slowly, usually as iodide and iodate, chiefly from the urine.

The *symptoms* after absorption are quite variable, probably because they are due to several different compounds of iodine, and usually delayed for some time, often 20 to 40 hours. Restlessness, anxiety, headache, insomnia, and general discomfort are followed by melancholy, hallucinations, and delirium, with rapid pulse and often a rise in temperature. There also may be nausea and vomiting, diuresis, and light convulsions. Death, which is ultimately due to general paralysis, is frequent after severe poisoning. Treatment by removing the iodoform unabsorbed may be sufficient, but generally the condition has progressed so far before the appearance of symptoms that the prognosis is unfavorable. Sodium bicarbonate is said to be beneficial, as are also saline injections.

Frequently individuals are subject to a *dermatitis* after iodoform. This resembles rhus poisoning and is probably but an idiosyncrasy similar to that from iodides.

Iodoform is *used* as a local application to wounds and abrasions on account of its antiseptic, stimulant, protective, hemostatic, and analgesic properties. The unique quality of this manifold effect is perhaps unsurpassed. It was at one time tried, like hundreds of other drugs, in tuberculosis and in syphilis but has been found useless. Although sometimes injected into tubercular joints, its internal administration should be avoided. The disadvantage of disagreeable odor and the danger of poisoning or idiosyncrasies have resulted in the introduction of hundreds of substitutes, of which aristol is a type. All of these are apparently non-toxic as local applications but are decidedly inferior; none seems to possess the peculiar action of iodoform on serous or mucous surfaces.

16. Formaldehyde

Solution of Formaldehyde (Formalin), U.S.P., B.P., N.R. An aqueous solution containing not less than 37 per cent of CH_2O, with variable amounts of methanol to prevent polymerization.

Formaldehyde, as a gas or in saturated solution, is a powerful *germicide*, probably equal to corrosive sublimate, and its volatility renders it more penetrable and in some ways more useful. Apparently it is very little toxic to higher animals. When inhaled, the gas is strongly irritant, so much so that continued breathing of it may bring about bronchial catarrh. Large doses by mouth cause the usual symptoms of gastro-enteritis and ultimate collapse. When applied locally to tissue, formaldehyde forms a peculiar protein combination, which is dense and insoluble; the skin is hardened, and the blood coagulated, thus giving astringent and styptic action. In more dilute form it prevents coagulation of egg albumin and milk and inhibits ferment action.

The gas is *used* to disinfect rooms, excreta, instruments, clothing, etc., for which it is very efficient. An infected room may be purified by mixing the formalin solution with potassium permanganate or other oxidizing agent and closing the room for 24 hours. Insects and vermin are not greatly affected. Temperatures above 15°C. are essential, and moisture is of great assistance. Applications to the body are not recommended, but they are sometimes used, greatly diluted, as an antiseptic in the eye, nose, or throat, occasionally as a hardening agent for the epidermis in excessive sweating, and sometimes as a preoperative disinfectant of the skin. As a food preservative formaldehyde is efficient, but the method is not harmless where unhealthy persons are concerned and is usually prohibited.

Paraformaldehyde has been administered by mouth for infections of the alimentary tract, a method that is considered of value, even if disagreeable.

Sodium formaldehyde sulfoxylate was introduced recently as an antidote for poisonings, especially by mercury.

17. Dyes

Acriflavine (Acriflavine Base, Neutral Acriflavine), U.S.P. A mixture of 2,8-diamino 10-methyl acridinium chloride and 2,8-diamino acridine.

Acriflavine Hydrochloride (Acriflavine, Trypaflavine), U.S.P., B.P.

Proflavine, N.R. 3,6-diamino acridinium monohydrogensulfate. $C_{13}H_{13}N_3SO_4 \cdot H_2O$.

Gentian Violet Medicinal, N.R. A mixture of penta- and hexa-methyl pararosaniline chlorides.

Soluble Fluorescein (Fluorescein Sodium, Resorcinolphthalein Sodium), U.S.P., B.P. The disodium salt of fluorescein, $C_{20}H_{10}O_5Na_2$.

Methyl-rosaniline (Crystal Violet, Gentian Violet, Methyl Violet), N.F. A mixture of hexamethyl-pararosaniline with other polymethyl derivatives in the form of chlorides.

The acridinium dyes are strongly *antiseptic* and comparatively non-toxic. They are claimed not to be weakened by the presence of serum, to be non-irritating, and to have no deleterious effect upon the leucocytes. Acriflavine is much slower in action and more antiseptic than proflavine. Solutions of either can be boiled without decomposition. They are used as lotions, irrigants, or dressings for wounds, burns, or ulcers, in the mouth (gingivitis), in the urethra, and in other places where they can be applied directly. The preparation employed is usually 1:1000 in saline, but for irrigation a weaker solution is preferable. Acriflavine is presumed to have a specific action on the gonococcus and is claimed to be very efficacious in treating gonorrhea.

Administered orally, both of the acridine dyes are excreted by the kidneys and give a bacteriostatic urine if the latter is maintained with an alkaline reaction. Although authorities have repeatedly cautioned against parenteral administration, it is often claimed that acriflavine can remedy various diseases by that route. Thus, it has been injected intravenously (1 cubic centimeter or more of 1 to 2 per cent) for rheumatism, undulant fever, psoriasis, meningitis, septicemia, scarlet fever, erysipelas, and gonorrhea. It would seem that the method is safe if properly carried out, but many poisonings have been reported.

Gentian violet seems to have a selective action on gram-positive organisms, although it is not a strong bactericide. It has been used in the treatment of wounds and infections of mucous and serous membranes, and especially of pleural and joint affections, by local application of 1:1000 to 1:500 solutions. It has also been employed in septicemia and other diseases by the intravenous injection of a 0.5 per cent solution. The method, which is based upon notable penetrability of the dye, may be still considered experimental.

Fluorescein is used as a diagnostic agent to detect foreign bodies or lesions on the cornea. A weak solution will not stain normal tissue, but abraded, ulcerated or diseased parts will be colored green, and foreign bodies will be surrounded by a green ring. Given by mouth or injection, the whole body may acquire a yellow color which, however, disappears within 24 hours. The cornea is affected in the same way as by local application.

The dye is also administered to test kidney function, about 20 grams being given on an empty stomach. Normally it appears in the urine in about 15 minutes and persists for about 40 hours. In renal disease the excretion is delayed and may last much longer. Excepting the general coloring of tissues, no side effects have been noted. It has also been used to diagnose cerebral meningitis.

Eosin, the beautiful tetrabrom derivative, has been employed in the form of salts to prevent shock from anaphylaxis and from injection of arsenicals.

It is claimed that organisms resistant to ultraviolet light are destroyed rapidly if first treated with fluorescein, eosin, or other dyes. This method has also been applied to the treatment of certain cancers, which may be thus more susceptible to irradiation.

Most of the aniline dyes are more or less bactericidal and often have selective action on certain species as well as unusual ability to penetrate readily into tissues. Several have found application in medicine to a limited extent. Azorubin and rose-bengal are sometimes administered to test liver function; erythrosine, as a diagnostic agent in cancer. Congo red, intravenously, is claimed to be remedial in hemorrhagic conditions, to counteract the poisonous effects of strychnine and curare, and to diagnose renal disease. Neutral red is by some preferred to histamine as a test for achylia gastrica, and it is also considered as a good test for pernicious anemia, because it is eliminated selectively by the oxyntic cell. Mercurochrome will be mentioned under discussion of the mercury compounds.

18. Sulfanilamide

Sulfanilamide (Prontylin), N.R. p-aminobenzenesulfonamide, $NH_2 \cdot C_6H_4 \cdot SO_2NH_2$. Dose: 0.8 to 1.0 Gm., 12 to 15 grains every six hours.

This synthetic has recently been introduced to treat systemic infections, especially those caused by betahemolytic streptococci. The first investigations of this action in 1935 were on an azo dye (prontosil) and its derivatives, but later several workers found that these substances are transformed in the body to sulfanilamide, which is the effective agent. It is used orally in doses of 15 grains or less per day for every 20 pounds weight up to 100 pounds, a maximum of 75 grains. This dose is divided into fourths every 6 hours.

The reported results have often been brilliant. The drug has been declared very successful in erysipelas, puerpural fever, septicemia from the hemolytic streptococci, streptococcic sore throat, and similar generalized infections. Several excellent results in infections by the meningococcus and by the gonococcus make it appear that sulfanilamide may become very useful in other types of disease.

Although the drug seems fairly safe by the oral route, some undesirable effects have been found, and parenteral therapy is still experimental. Acidosis, which may be counteracted by sodium bicarbonate, jaundice, and urticaria, have been encountered frequently, and hemolytic anemia and granulocytopenia, so often a sequel from benzene derivatives, sometimes. Serious sulfhemoglobinemia and methemoglobinemia will occasionally follow extended administration, the former almost certainly if magnesium sulfate is used simultaneously.

THE ALIMENTARY TRACT

INTESTINAL ANTISEPTICS

Although many drugs having antiseptic properties have been administered by mouth to secure freedom from intestinal *putrefaction,* it has become increasingly evident that such an object cannot be fully attained. There is little chance to destroy the many bacteria in the bowel or even to reduce them appreciably, without harm to the host tissue. The large mass of material tends to dilute the poison; the latter is generally absorbed readily to give toxicity; and the bacteria are usually well imbedded in the walls. A limitation of abnormally increased action is all that can be expected, and even this is unsatisfactory.

The *best measures* to reduce putrefaction are diet and purgation, which are usually as efficient as is possible. If drugs are to be used, they must be selected for insolubility in upper parts of the tract. The ideal substance should have maximum bactericidal character, combined with minimum solubility and absorption, and should be free from irritating effects. Many have been tried at one time or another, and but few have survived. At present greatest reliance is placed on salol, naphthol and other phenols, and mercury purges.

1. Salol

Phenyl Salicylate (Salol), U.S.P. $C_6H_4(OH)COOC_6H_5$ 1:2. Dose: 0.3 Gm., 5 grains; maximum 30 grains.

Tablets of Phenyl Salicylate, N.F.

Salol was introduced in 1886 as an inert substance designed to be split up in the intestine to give phenol and salicylic acid, in order to give asepsis. The drug itself has no action, nor does it hydrolyze when applied externally. The intestinal decomposition was not so efficient as expected, owing to rapid absorption of the products. The effects after absorption are those of the salicylates, although occasionally serious phenol poisoning has been observed, and the urine is always darkened. After large doses symptoms from both substances are met.

Salol is considered by some as the best **intestinal antiseptic** available and is probably as efficient as any, although many investigators report no results whatever. Owing to the salicylic acid excreted, it is claimed excellent as a urinary antiseptic, particularly in chronic cystitis. Externally there is no action, for salol is not hydrolyzed in a wound or by bacteria to any great extent, but it serves as an inert powder like iodoform. As a remedy in rheumatism and for fever, it is inferior to the other salicylates and may give rise to poisoning.

2. Betanaphthol

Betanaphthol (Naphthol), U.S.P., B.P. Beta-monohydroxy naphthalene $C_{10}H_7OH$. Dose: 0.25 Gm., 4 grains, U.S.P.; maximum 15 grains.

Betanaphthol Benzoate (Benzonaphthol), N.R. Dose: 0.2 to 0.5 Gm.

Betanaphthol Salicylate, N.R. Dose: 0.3 to 0.5 Gm.

Betanaphthol is similar to phenol in *action* but less irritating and more antiseptic. The absorbed portion tends to destroy red corpuscles and may cause severe nephritis. Frequent injuries to the retina and increased opacity of the lens are also observed. Betanaphthol has been *used* considerably as an intestinal antiseptic, where its utility is limited by the danger of poisoning. The local discomfort may be counteracted by converting to esters like salol, of which the salicylate and benzoate are types. Betanaphthol and its esters are also employed as external antiseptics, especially on the scalp in 1 to 2 per cent solution. Some say that there is no better remedy for diseases of the hair roots. It is also used for various parasites and to combat hookworm; for the latter it is fairly efficient but is usually considered inferior to thymol and carbon tetrachloride.

Alphanaphthol is sometimes used in the same way as the beta isomer.

ANTACIDS

The antacids are materials capable of uniting with acid. This action takes place usually in the alimentary tract, although remote effects may be desired and secured. The neutralization of acid in the stomach draws upon the balance within the body, so that there is in all parts an increase of potential alkalinity. Thus the antacids are said to alkalinize the blood and urine, a statement which is often literally untrue but indirectly correct. These drugs may be *used,* therefore, to relieve the pain and dispel the gas of hyperacidity; to counteract the effects of mineral acids in poisoning; and to render the blood, urine, and other body fluids of greater alkalinity in acidosis, rheumatism, etc.

1. Alkali Bicarbonates

Sodium Bicarbonate (Soda), U.S.P., B.P. $NaHCO_3$. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Sodium Bicarbonate, N.F.

Potassium Bicarbonate, U.S.P., B.P. $KHCO_3$. Dose: 1 Gm., 15 grains, U.S.P.

The high value of these salts depends upon their ability to neutralize acids and to exert a mild irritant action and upon their osmotic effects in common with other soluble substances. Some of the applications are difficult to explain. The sodium salt is generally preferred.

The most important *uses in medicine* are antacid and local stimulant or sedative externally, diuretic and expectorant, and for acidosis and rheumatism. The action on skin and mucous membranes is almost nil, and yet the very mild irritation is sufficient to relieve the pains of burns and bites and to create a mild stimulation in skin diseases, ulcers, and burns, as well as to dissolve catarrhal mucus in the bronchi and stomach. In excessive acidity, the neutralizing ability will relieve heartburn, gastric flatulence, and other dyspepsias, and the alkaline character also often ameliorates conditions which are not caused by too much acid, by dissolving abnormal products which interfere with the usual course of digestion. The bicarbonates render the urine alkaline and increase the total output, effects which may be useful in infectious diseases of the bladder and urethra and in preventing the formation of urate calculi. The advantages under such conditions led to the use in rheumatism and gout, where there seems to be much benefit that cannot be explained in the light of our present knowledge. Although sodium bicarbonate has no effect directly on the oxidation and utilization of sugar, it is apparently useful in diabetes, probably by furnishing a more alkaline medium which may favor glucose metabolism. Furthermore, the acidosis characteristic of this and many other diseases is checked by very large doses, frequently repeated. Finally, this salt also is advantageous as a medium to replace blood after operation or hemorrhage, being sometimes preferable to saline infusions. For the purpose it is injected in 1.5 per cent solution intravenously, with the precaution that it is not boiled and does not contain very much carbonate, which is caustic. There are many other minor applications of the bicarbonates which make them very useful medicinal agents.

2. Lime

Calcium Oxide (Calx, Lime, Quicklime), N.F. CaO.

Calcium Hydroxide (Slaked Lime), U.S.P., B.P. $Ca(OH)_2$.

Solution of Calcium Hydroxide (Lime Water), U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.

Lime Liniment (Carron Oil), N.F.

Quicklime and the hydroxide are cheap substances sometimes used to disinfect animal or vegetable debris. They are not so caustic as sodium or potassium hydroxide, so are frequently mixed with them in order to limit their actions as escharotics. In the form of lime water, calcium hydroxide unites with carbon dioxide to give a protective and sedative layer of carbonate, and there may be some astringency on mucous membranes and abraded surfaces. This is used to combat diarrhea, as with bismuth, also externally on burns in the form of lime liniment. As an antacid lime water is mild because it is very dilute; for this reason it may be added to infants' food to prevent coagulation of casein in large lumps. Syrup of lime is considered a fairly efficient antidote for phenol, with which it forms an insoluble phenate; lime water is too dilute.

3. Calcium Carbonate

Precipitated Calcium Carbonate (Precipitated Chalk), U.S.P., B.P. $CaCO_3$. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Calcium Carbonate, N.F.

Prepared Chalk (Creta Præparata, Drop Chalk), U.S.P., B.P. A native form of calcium carbonate freed from most of its impurities by elutriation. Dose: 1 Gm., 15 grains, U.S.P.

Compound Chalk Powder, U.S.P. Dose: 2 Gm., 30 grains.

Chalk Mixture, U.S.P. Dose: 15 cc., 4 fluidrachms.

Aromatic Chalk Powder, N.F., B.P. Dose: 2 Gm., 30 grains, N.F.

Precipitated Calcium Phosphate, N.F., B.P. $Ca_3(PO_4)_2$. Dose: 1 Gm., 15 grains, N.F.

All these preparations can neutralize active acidity in the stomach and counteract excessive amounts as in indigestion. When thus neutralized, the calcium is converted to chloride and, hence, may be used as are other salts of the metal. Chalk and calcium carbonate are good dusting powders and often form the basis of tooth powders and pastes. The phosphate has been employed as an efficient antacid with the reputed advantage over magnesium hydroxide and bicarbonate that, being insoluble, it does not produce systemic alkalinization.

Other Antacids

The hydroxides and carbonates of the alkali metals, as well as those of ammonium, may be used after dilution. Magnesium oxide and carbonate are probably the most popular, while zinc oxide and bismuth subcarbonate are sometimes so applied. The salts of organic acids are oxidized within the body to carbonates and can thus increase the alkaline reserve. For alkalinizing the blood and urine the most useful are acetates, citrates, and tartrates.

EMETICS

The emetics are drugs which cause an expulsion of the stomach contents. They may do this by a local action upon the tract, which is probably reflex, or by direct stimulation of the vomiting center. Most emetics belong to the first class. Accompanying the vomiting is a series of symptoms more or less severe, which may or may not be secondary. There is a feeling of sickness and depression, weakness of the muscles, paleness, an increase in the secretion of sweat, saliva, tears, and bronchial mucus, and an after-depression, which with some drugs may be lacking. Emesis is employed to expel poisonous drugs; in indigestion from overeating; to remove obstructions in the bronchial passage; to cut short asthmatic attacks; and illogically to aid in ejecting obstructions of the bile ducts, by compression. The only drug used chiefly for the purpose is apomorphine which is preeminent as an emetic.

Apomorphine

Apomorphine Hydrochloride, U.S.P., B.P. The hydrochloride of an alkaloid, $C_{17}H_{17}NO_2$, prepared from morphine. Dose: expectorant 0.001 Gm., 1/60 grain; emetic, hypodermic 0.005 Gm., 1/12 grain, U.S.P.; maximum 1/4 grain.

Tablets of Apomorphine Hydrochloride, N.F.

Apomorphine, although obtained from morphine, is entirely different from the latter in *physiological properties.* Small doses stimulate the central nervous system, especially the vomiting center, giving emesis quickly and certainly. This is entirely a central action, because it is not prevented by bismuth or other local drugs; because the effect is more rapidly obtained by hypodermic injection; and because it is prevented by narcotics. Under certain conditions, doses too small to be emetic give a hypnotic action but not normally. Large amounts give delirium and convulsions, then asphyxia.

The drug is *the most reliable emetic*, administered either by mouth or hypodermically, action taking place within a few minutes. It is less useful as a nauseant but sometimes prescribed in expectorant mixtures. In alcoholism it is said to be a good sedative, as also in hysteria, strychnine poisoning, and eclampsia.

Other Emetics

Those drugs which are important to produce vomiting are warm water, salt, mustard, zinc or copper sulfates, alum, and vegetable bitters, all of which act locally; ipecac, tartar emetic, senega, and squill, which may be active in both ways. In addition, ammonium salts, soap, lobelia, stillingia, tobacco, sarsaparilla, baptisia, sanguinaria, etc., have been employed. Any irritation of the fauces will tend to produce the action, so that a large number of other materials might be used.

ANTIEMETICS

The drugs used to prevent vomiting are of two classes: those which have central action, and those causing their effects locally. Morphine, chloral, bromides, and alcohol are the best of the former group. Bismuth, demulcents, ice, lime water, arsenic, local anesthetics, and carbonated drinks belong to the second. The counteraction of nausea at times can be accomplished only when one understands the cause, since it is merely a symptom and not a disease. Usually the local remedies are sufficient.

PURGATIVES

Purgatives are drugs which facilitate evacuation of the intestinal contents. They are the most ancient of remedies, being considered in the older days as synonymous with therapy, and even today they are employed to an extent which is probably irrational.

Although some of them may act after hypodermic administration by being excreted into the intestine, the usual route is the oral one, because the *action is entirely local.* A few, such as agar, accomplish the purpose by increasing the bulk of feces. Others like petrolatum lubricate and mechanically prevent water absorption. The salines interfere with this absorption by osmotic action, but the majority of purgatives act by irritation. Almost any irritant will succeed in producing bowel movement, but those used differ in being mild and in not exerting the stimulating action until the site of demand is reached. The mechanical excitation increases peristalsis, thus hastening the progress of food residues and, by shortening the sojourn, decreasing the amount of water absorption. There may also be some increase of secretions from the intestinal glands, but this has not been clearly demonstrated. There may be some pain during the process, attributable to the irritation and to the abnormal activity. With most of the purgatives, there is more or less congestion. It has been presumed that the more active drugs actually draw water from the body, being thus beneficial in edemas but, except with those which are strong enough to form inflammations analogous to external blistering, this is doubtful. There is a tendency, however, to withdraw liquid from the body by other channels, even with a decrease in water absorption, so that results amount to the same thing.

The *ideal purgative* would be a bland substance which did not interfere with normal processes in the upper digestive tract and remained unabsorbed until it reached the large intestine, where it would exert a mild irritation sufficient for the purpose. The crude drugs, containing a large amount of inert material to prevent absorption, are more suitable than the isolated principles. Some of the substances used are not active until they come in contact with alkali or bile. Among others of this class are jalap, scammony, and podophyllum. In large doses the strong purgatives never give more toxic results than an excessive inflammation of the intestinal walls and never cause nephritis, but in pregnancy they are very liable to produce abortion.

The purgatives are used for a large *number of purposes*, among which may be listed: (1) to relieve acute or chronic constipation; (2) to soften stools in hemorrhoids; (3) to cleanse intestines of foreign irritants; (4) to remove poisons from the body; (5) to relieve the kidneys in nephritis; (6) to favor the absorption or withdrawal of dropsies; (7) to lower temperature in fever; (8) to relieve internal congestions of various kinds; (9) to increase bile flow (irrational); (10) to decrease weight in obesity by interfering with metabolism (illogical).

Among the factors that influence the *choice of drug* are the time for administering, the period to elapse before action is desired, and the health of the alimentary mucosa. Salines act in ½ to 1 hour, castor oil in 1 to 2 hours, jalap in 3 hours or less, senna 5 hours, phenolphthalein 8 hours, cascara 8 to 12 hours, and podophyllum 10 to 18 hours, although these periods may vary with individuals. There is also considerable difference in the reaction of various persons to one and the same drug. Thus phenolphthalein may often be mild toward children in 2 to 3 grain doses, which would be much more than enough to cause violent retching with certain adults. Children are as a rule less susceptible to purgatives than are older persons.

Any detailed *classification* of purgatives on the basis of degree must be arbitrary, because dosage and dilution modify this degree to a marked extent. From time immemorial such divisions have been attempted and various names assigned to the classes so bounded. Thus we have: laxatives (looseners); evacuants; aperients (openers); lenitives (softeners); hydragogues (water drawers); eccoprotics (dung excreters); cathartics (cleansers); drastics (strong); purgatives (cleansers). All of them, however, fall into three classes which are sufficiently distinct: the salines, which act by osmosis; the milder drugs, which may be called laxatives; the active cathartics. The last class includes those termed drastics, which are much more powerful than substances like castor oil. Pharmacological classifications have also been attempted, but a description of these would serve no purpose here.

SALINES

1. Magnesium

Magnesium Oxide (Light Magnesia), U.S.P., B.P. MgO. Dose: antacid 0.25 Gm., 4 grains, laxative 3 Gm., 45 grains, U.S.P.

Heavy Magnesium Oxide (Heavy Magnesia), U.S.P., B.P. Dose: as above.

Magnesia Magma (Milk of Magnesia, Mixture of Magnesium Hydroxide), U.S.P., B.P. Dose: antacid 4 cc., 1 fluidrachm, laxative 15 cc., 4 fluidrachms, U.S.P.

Plant's Magnesia Wafers, N.R.

Magnesium Carbonate (Light Magnesium Carbonate), U.S.P., B.P. A mixture of hydrated magnesium carbonate and magnesium hydroxide. Dose: antacid 0.6 Gm., 10 grains, laxative 8 Gm., 2 drachms, U.S.P.

Heavy Magnesium Carbonate, B.P.

Solution of Magnesium Bicarbonate (Fluid Magnesia), B.P.

Carminative Mixture (Dalby's Carminative), N.F. Dose: for infants 0.5 cc., 8 minims.

Solution of Magnesium Citrate (Citrate of Magnesia), U.S.P. Dose: 200 cc., 7 fluidounces.

Magnesium Sulfate (Epsom Salt), U.S.P., B.P. $MgSO_4 \cdot 7H_2O$. Dose: 15 Gm., 4 drachms, U.S.P.

Effervescent Salt of Magnesium Sulfate, N.F., B.P. Dose: 16 Gm., 4 drachms.

Ampuls of Magnesium Sulfate, N.F. Dose: 2 cc. (about 1 Gm.).

Artificial Vichy Salt, N.F.

Effervescent Artificial Vichy Salt, N.F. Dose: 4 Gm., 60 grains.

Artificial Kissingen Salt, N.F. Dose: 1.5 Gm., 22 grains.

Effervescent Artificial Kissingen Salt, N.F. Dose: 4 Gm., 60 grains.

Tribasic Magnesium Phosphate, N.R. $Mg_3(PO_4)_2 \cdot 7H_2O$. Dose: 1 to 5 Gm.

Magnesium sulfate has a sedative effect when applied in saturated solution, but, in general, the salts of this metal have no local action on the skin. In the alimentary tract they are absorbed with difficulty and excite only purgation. At the same time, the carbonate, hydroxide, and oxide neutralize any acid with which they come in contact. Injected into the circulation, magnesium depresses all muscles and the central and peripheral nerves, being in most respects antagonistic to calcium. In this depressant action it resembles potassium, except that the latter affects mostly the heart, while magnesium causes death by respiratory failure. With doses very close to those which are fatal, magnesium sulfate hypodermically gives complete anesthesia, which has as yet been unexplained. Intraspinally, this effect can be utilized like cocaine, and combinations with other anesthetics have been proposed.

All magnesium compounds can be *used* as laxatives, but some of them, like the nitrate, are readily absorbed to give toxicity. The carbonate, magma, and oxide are of less efficiency than the sulfate but have the advantage of being antacid. In fact the usual aim in using them is to relieve dyspepsia, nausea, heartburn, sick headache, rheumatic and gouty pains, and other complaints attended with acidity, purgation being merely an additional quality. For these applications they are usually combined with other drugs. The carbonate may cause some flatulence from carbon dioxide, but the oxide is free from this possibility and is non-irritating. Both have been employed as dusting powders and pastes for ulcers and burns. The oxide is considered an antidote for arsenic poisoning. Magnesium citrate solution is a popular and agreeable laxative, and magnesium phosphate has been introduced as an antacid with the advantage of not causing systemic alkalinization.

The **sulfate** is applied locally in saturated solution to relieve pain and discomfort in inflammations, burns, erysipelas, rheumatism, sprains, and bruises. It is presumed to be somewhat antiphlogistic by promoting the absorption of inflammatory products. The *anesthetic* character has been utilized intravenously against tetanus, eclampsia, chorea, hypertension, asthma, whooping cough, and strychnine poisoning, but it is very dangerous. Magnesium has also been found to synergize morphine or ether, the sulfate being given by hypodermic injection. The dose used is sufficient and yet far below that which is dangerous.

2. Sodium Phosphate

Sodium Phosphate, U.S.P., B.P. $Na_2HPO_4 \cdot 12H_2O$. Dose: 4 Gm., 1 drachm, U.S.P.

Exsiccated Sodium Phosphate, U.S.P. Dose: 2 Gm., 30 grains.

Effervescent Sodium Phosphate, U.S.P., B.P. Dose: 10 Gm., 2½ drachms, U.S.P.

Solution of Sodium Phosphate, N.F. Dose: 8 cc., 2 fluidrachms.

Sodium Biphosphate (Acid Sodium Phosphate, Primary Sodium Phosphate), U.S.P., B.P. Dose: 0.6 Gm., 10 grains, U.S.P.

Sodium phosphate is often prescribed as a laxative, especially for children, on account of its mild action and agreeableness. The effervescent salt is particularly pleasing to many, or it may be mixed with food to disguise its taste. A former reputation for stimulation of biliary flow is now known to be based on erroneous information, yet it is frequently so used. All of the phosphates have been given in rickets and other bone diseases under the irrational assumption that the element phosphorus is lacking. They have also been administered for years in nervous diseases on the theory that these are also due to deficiency of the element, but they are now considered clinically worthless for this object.

Primary sodium phosphate is acid in reaction and neutralizes alkali in the intestine. The reserve alkali of the blood is thus drawn upon, and the balance is maintained by excretion of acid in the urine. With sufficient amounts, therefore, sodium biphosphate is capable of maintaining an acid urine and is useful to aid methenamine which requires such a condition. In large doses the salt is laxative.

3. Tartrates

Potassium and Sodium Tartrate (Rochelle Salt), U.S.P., B.P. $NaKC_4H_4O_6 \cdot 4H_2O$. Dose: 10 Gm., 2½ drachms, U.S.P.

Compound Effervescing Powder (Seidlitz Powder, Effervescent Tartrated Soda Powder), U.S.P., B.P.

Potassium Bitartrate (Cream of Tartar, Acid Potassium Tartrate), U.S.P., B.P. $KHC_4H_4O_6$. Dose: 2 Gm., 30 grains, U.S.P.

The bitartrate combines the part of a refreshing, acid drink with cathartic, diuretic, antilithic, and mild alkalizing effect. It is similar to tartaric acid in action and can cause analogous poisoning, since an ounce or two has caused death. All of the tartrates are more easily absorbed than the other salines and hence have less purgative and more diuretic effect, but they are used as mild aperients. Like other organic salts, they have a tendency to increase potential alkalinity but have relatively low activity in this respect. They have no more cholagogue action than other purges, notwithstanding former reputation. Seidlitz powder makes an agreeable mild laxative.

4. Sodium Sulfate

Sodium Sulfate (Glauber's Salt), U.S.P., B.P. $Na_2SO_4 \cdot 10H_2O$. Dose: 15 Gm., 4 drachms, U.S.P.

Exsiccated Sodium Sulfate, N.F. Dose: 8 Gm., 2 drachms.

Artificial Carlsbad Salt, N.F. Dose: 1 Gm., 15 grains.

Effervescent Artificial Carlsbad Salt, N.F. Dose: 4 Gm., 60 grains.

Effervescent Sodium Sulfate, B.P.

Potassium Sulfate, N.F. K_2SO_4. Dose: 1 Gm., 15 grains.

Sodium sulfate is less popular as a purgative, not because of small efficiency but on account of its disagreeable taste. It is used considerably in veterinary practice and has some reputation in the treatment of gall stones and in biliary insufficiency. The taste may be corrected to some extent by acids and effervescing mixtures.

Potassium sulfate might be used in the same way, but larger doses have the depressant action of potassium. Both may be given as part of the treatment for phenol poisoning because, although not antidotal, they are harmless and promote defecation.

LAXATIVES

1. Castor Oil

Castor Oil, U.S.P., B.P. The fixed oil obtained from the seeds of *Ricinus communis* (*Euphorbiaceæ*). Dose: 15 cc., 4 fluidrachms, U.S.P.

Aromatic Castor Oil, N.F. Dose: 15 cc., 4 fluidrachms.

Castor oil itself is *bland* and *inert* but contains a glyceride of ricinoleic acid, the salts of which are actively purgative. Since these are formed only whenever the fat is saponified, the oil is usually similar to olive and cottonseed oils. In the small intestine, however, the sodium salt is produced to give mild irritation and a stimulation of peristalsis, resulting in a bowel movement that is certain and complete. In fact the evacuation may be so complete that a subsequent one does not take place for many hours.

It is a very *important purgative* because it causes a minimum of irritation and colic and little hyperemia and can thus be used under most conditions, even where active inflammation exists. If employed continuously there may be some disturbance of digestion, notwithstanding the fact that in some localities (China) the oil is often an article of diet. It is best administered on an empty stomach, alone or flavored to disguise the disagreeable taste. The only really efficient method for preventing recognition of this taste is to administer in capsules, but the size of the dose is inconvenient.

Castor oil is sometimes *applied* to wounds, burns, and abscesses as an emollient and as a vehicle for applications to the eye. It is also an ingredient of many hair oils.

The seed coats of *Ricinus communis* contains a very toxic albumin, **ricin,** which does not enter into the oil during manufacture, but which is sometimes the cause of poisoning. The symptoms, which are often delayed some time, are violent gastroenteritis, feeble pulse, profuse sweating, thirst, great weakness, and convulsions. The treatment would consist in evacuation and the administration of stimulants if necessary.

Sodium ricinoleate (soricin) has been recommended as a detoxifying agent and detergent in the mouth and intestines.

2. Agar

Agar (Agar-agar), U.S.P., B.P. The dried mucilaginous substance extracted from *Gelidium corneum* and other species of *G.* and closely related algæ (*Rhodophyceæ*). Dose: 10 Gm., 2½ drachms, U.S.P.

Agar consists mainly of gelose, a hemicellulose which is very little digestible by man (10 per cent) and nearly tasteless. It gelatinizes with water which it absorbs in quantity. In the intestinal tract, this results in water retention by imbibition and increase in bulk, making the feces larger and softer. It is generally administered with some other purgative, such as petrolatum, phenolphthalein, or cascara. It can be used like gelatin or chondrus as a demulcent.

3. Tamarind

Tamarind, B.P. The fruits of *Tamarindus indica* (*Leguminosæ*), freed from the brittle outer part of the pericarp and preserved with sugar.

This drug probably owes its activity to salts and organic acids, also to its ability to absorb water. It is sometimes used as a refrigerant and mild laxative for children but is usually mixed with stronger purgatives, as in confection of senna.

4. Manna

Manna, N.F. The dried exudation of *Fraxinus Ornus* (*Oleaceæ*). Dose: 15 Gm., 4 drachms.

Manna contains principally mannite, a difficultly absorbable alcohol which acts on the intestinal contents similarly to the salines. It may be given as an infusion or a syrup for a mild laxative. It is contained in compound infusion of senna.

5. Cassia

Cassia (Cassia Pulp), B.P. The pulp of the fruit of *Cassia Fistula* (*Leguminosæ*).

Cassia is similar in composition to tamarind, being a useful laxative in small doses. In larger ones, it is liable to cause nausea and griping, so it is generally given in combination with other drugs.

6. Psyllium

Plantago Seed (Psyllium Seed, Plantain Seed), N.F., N.R. The cleaned, dried, ripe seed of *Plantago Psyllium* or of *P. arenaria*, known in commerce as Spanish or French Psyllium Seed; or of *P. ovata*, known in commerce as Blonde Psyllium or Indian Plantago Seed (*Plantaginaceæ*). Dose: 8 Gm., 2 drachms, N.F.

This drug contains mucilaginous substances which are indigestible and which cause mild laxative action. It may be irritating if not accompanied by enough water.

Prunes and figs are edible fruits which are mildly laxative and demulcent and are used in folk medicine for constipation. They are sometimes used in commercial mixtures with other purgatives.

CATHARTICS

1. Cascara

Cascara Sagrada (Sacred Bark, Rhamnus Purshiana), U.S.P., B.P. The dried bark of *Rhamnus Purshiana* (*Rhamnaceæ*). Dose: 1 Gm., 15 grains, U.S.P.

Extract of Cascara Sagrada, U.S.P., B.P. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 10 grains.

Fluidextract of Cascara Sagrada, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.

Aromatic Fluidextract of Cascara Sagrada, U.S.P. Dose: 2 cc., 30 minims.

Elixir of Cascara Sagrada, N.F., B.P. Dose: 4 cc., 1 fluidrachm, N.F.

Compound Pills of Cascara (Hinkle's Pills), N.F.

Frangula (Buckthorn Bark), N.F. The dried bark of *Rhamnus Frangula* (*Rhamnaceæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Frangula, N.F. Dose: 1 cc., 15 minims.

Rhamnus Cathartica (Buckthorn Berries, Baccæ Spinæ Cervinæ), N.F. The dried, ripe fruit of *R. Cathartica* (*Rhamnaceæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Rhamnus Cathartica, N.F. Dose: 1 cc., 15 minims.

Cascara gives, by action in the large intestine, a softened stool accompanied by little or no griping and has become a very popular remedy for chronic constipation. The active components are cascarin and isoemodin which are anthraquinone derivatives. It is said that susceptibility is not lost by continued use, so that the drug may be gradually withdrawn as new habits are formed. The fresh drug is claimed to cause vomiting and malaise, untoward properties which disappear by ageing or by heating. The pharmacopœia, therefore, orders that it be stored at least 1 year before use, but several investigators have failed to substantiate the necessity for doing this. In small doses cascara acts as a simple bitter tonic and is sometimes prescribed for the purpose.

Frangula and rhamnus cathartica are similar to cascara but less available, probably less efficient, and certainly not so popular. They are gradually being abandoned. Rumex (curved or yellow dock), which contains anthraquinone derivatives of a similar nature, was formerly much employed as alterative in skin diseases and syphilis, but its only known medicinal value is based upon mild laxative action.

2. Rhubarb

Rhubarb (Rheum), U.S.P., B.P. The dried rhizome and roots of *Rheum officinale* or of *R. palmatum* (*Polygonaceæ*) or of other species or hybrids of *R.* grown in China and Tibet, deprived of periderm tissues. Dose: 1 Gm., 15 grains, U.S.P.

Extract of Rhubarb, U.S.P. Dose: 0.5 Gm., 8 grains; maximum 10 grains.

Fluidextract of Rhubarb, N.F. Dose: 1 cc., 15 minims.

Aromatic Tincture of Rhubarb, U.S.P. Dose: 4 cc., 1 fluidrachm.

Compound Tincture of Rhubarb, N.F., B.P. Dose: 4 cc., 1 fluidrachm, N.F.

Sweet Tincture of Rhubarb, N.F. Dose: 4 cc., 1 fluidrachm.

Syrup of Rhubarb, N.F. Dose: 10 cc., 2½ fluidrachms.

Aromatic Syrup of Rhubarb, U.S.P. Dose: 10 cc., 2½ fluidrachms.

Compound Pills of Rhubarb, N.F., B.P.

Compound Powder of Rhubarb (Gregory's Powder), N.F., B.P. Dose: 2 Gm., 30 grains, N.F.

Compound Mixture of Rhubarb (Mixture of Rhubarb and Soda), N.F. Dose: 4 cc., 1 fluidrachm.

Alkaline Elixir of Rhubarb (Neutralizing Cordial), N.F. Dose: 4 cc., 1 fluidrachm.

Rhubarb, one of the oldest of remedies, contains glucosides of tannins, which are astringent; and resinous anthraquinone derivatives, which are purgative. In small doses the astringent action predominates and can be used for diarrhea and other intestinal disorders and as an astringent bitter. In larger amounts the laxative properties are shown in a movement after 6 to 10 hours, with little or no colic. Rhubarb is, therefore, considered suitable for chronic constipation of children and of weakened patients. It may cause vomiting and headache and sometimes skin eruptions, circumstances which make it less popular than formerly. The urine is often colored yellow or brown, changed by alkalies to red. Some of the official preparations are superfluous.

Juglans (butternut bark) appears to act like rhubarb and is sometimes used as a remedy in habitual constipation.

3. Aloe

Aloe (Aloes), U.S.P., B.P. The dried juice of the leaves of *Aloe Perryi*, known in commerce as Socotrine Aloe, or of *Aloe vera*, known in commerce as Curaçao Aloe (*Liliaceæ*). Dose: 0.25 Gm., 4 grains, U.S.P.

Aloin, U.S.P., B.P. A pentoside or mixture of pentosides obtained from aloe. Dose: 0.015 Gm., ¼ grain, U.S.P.

Pills of Aloe, U.S.P., B.P.

Pill of Aloe and Asafetida, B.P.

Pill of Aloe and Iron, B.P.

Pills of Aloe and Mastic (Lady Webster Dinner Pills), N.F.

Pills of Aloe and Myrrh, N.F.

Tincture of Aloe, N.F. Dose: 2 cc., 30 minims.

Tincture of Aloe and Myrrh, N.F. Dose: 2 cc., 30 minims.

Extract of Aloe, N.F. Dose: 0.125 Gm., 2 grains.

Pills of Aloin, Strychnine and Belladonna, N.F.

Pills of Aloin, Strychnine, Belladonna and Cascara, N.F.

Pills of Aloin, Strychnine, Belladonna and Ipecac (Compound Laxative Pills), N.F.

Aloe *contains* a variable mixture of extremely bitter pentosides (10 to 15 per cent) which are inactive in themselves, but which are hydrolyzed slowly in the presence of alkalies into emodin or similar active anthraquinone derivatives. This cleavage seems to be promoted by bile and by iron salts, although the presence of bile does not appear essential. Aloin contains at least some of these crystalline glucosides but is usually not entirely representative of aloe action.

Aloe is a very old remedy, having been used by the Egyptians centuries ago. In *very small doses* it has been given as a stomachic, especially with iron, whose constipating tendency is thus counteracted. In somewhat *larger doses* it is laxative and, in the usual amounts, strongly so. The hydrolysis occurs only after some time and never before the colon is reached. The action is mildly severe, being very apt to produce griping, which may be prevented by combining with belladonna or carminatives. Since this strong action would be expected to produce considerable congestion, aloe is to be avoided in hemorrhoids, menstruation, or pregnancy. Indeed, the drug is sometimes prescribed as an emmenagogue. It is said that continual use of aloe does not lead to lessened efficiency and that it is of particular value in habitual constipation, but it probably has no advantage over cascara. Hypodermic administration is also effective because the glucosides are excreted into the intestines, but the method is painful, and nothing is gained. In rabbits, subcutaneous administration leads to fatal nephritis.

An alcoholic solution of aloe is said to give relief in bee stings, and the leaves have been employed for burns from X-ray and for ulcers.

Several synthetic anthraquinone derivatives have been marketed without ever becoming popular, because they cannot possess much advantage over the emodin drugs. Purgatin, or purgatol, is anthrapurpurin diacetate; and exodin is a methyl ester of diacetyl hexahydroxy anthraquinone.

4. Senna

Senna, U.S.P., B.P. The dried leaflets of *Cassia Senna,* known in commerce as Alexandria Senna, or of *Cassia angustifolia,* known in commerce as Tinnevelly Senna (*Leguminosæ*). Dose: 2 Gm., 30 grains, U.S.P.

Fluidextract of Senna, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Syrup of Senna, U.S.P., B.P. Dose: 8 cc., 2 fluidrachms, U.S.P.

Compound Senna Powder (Compound Licorice Powder), U.S.P. Dose: 4 Gm., 1 drachm.

Infusion of Senna with Magnesium Sulfate, N.F. Dose: 60 cc., 2 fluidounces.

Infusion of Senna (fresh and concentrated), B.P.

Confection of Senna, B.P.

Compound Mixture of Senna (Black Draught), B.P.

Senna Fruit, B.P. The dried ripe fruits of *Cassia acutifolia* and of *Cassia angustifolia.*

Senna is the most drastic of the emodin drugs, causing more or less griping with moderate doses and a series of watery stools if the amount is larger. Like most of them, it can be given hypodermically without any great advantage. It is especially suitable for acute obstruction, but several of its preparations, notably compound licorice powder, are employed in the habitual constipation of children. Because of the griping, senna is most often combined with aromatics or carminatives.

5. Phenolphthaleins

Phenolphthalein, U.S.P., B.P. $(C_6H_4OH)_2CO \cdot C_6H_4CO$. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Tablets of Phenolphthalein, N.F.

Phenolphthalein Agar, N.R. Dose: 1 gram twice daily.

Emulsion of Liquid Petrolatum with Phenolphthalein, N.F. Dose: 15 cc., 4 fluidrachms.

Isacen, N.R. Diacetyl dihydroxyphenylisatin. Dose: 5 to 20 mg.

Phenolsulfonphthalein (Phenol Red), U.S.P., N.R. $(C_6H_4OH)_2CO\text{-}C_6H_4SO_2$. Dose: 0.006 Gm., $\frac{1}{10}$ grain by intravenous injection, U.S.P.

Phenoltetrachlorphthalein, N.R. A dibasic dye formed by the condensation of phenol and tetrachlorphthalic acid or its anhydride. Dose: 0.05 to 0.4 gram.

Soluble Iodophthalein (Tetraiodophenolphthalein Sodium, Tetiothalein Sodium, Iodeikon), U.S.P., B.P. The disodium salt of tetraiodophenolphthalein. $NaOOC \cdot C_6H_4C : C_6H_2I_2OC_6H_2I_2ONa$. Dose for each 10 kilograms of body weight: orally 0.5 Gm., 8 grains; intravenously 0.3 Gm., 5 grains, U.S.P.

Phentetiothalein Sodium (Sodium Phenoltetraiodophthalein, Iso-iodeikon), N.R. $NaOOC \cdot C_6H_4C:C_6H_4O \cdot C_6H_4ONa$. Dose: 0.04 Gm. per kilogram of weight; maximum 2.5 Gm.

Sodium Phenoltetrabromphthalein Sulfonate (Bromsulphalein), N.R. $O \cdot CO \cdot C_6Br_4C(C_6H_3OH \cdot SO_3Na)_2$. Dose: 2 mg. per kilogram intravenously.

Phenolphthalein is insoluble and inactive on normal mucous membrane but becomes mildly purgative in the presence of alkali in the intestine. The exact nature of this action, discovered in 1900, is not well understood. It takes place partially in the small, more in the large, bowel. Some of the drug is absorbed and returned with the bile, but 85 per cent is excreted in the feces. Hypodermically in olive oil, or even intravenously, it gives no toxic symptoms, being excreted unchanged by the liver, less by the urine, sweat, tears, etc. In the intestine it is absorbed partly and returned to the bile. Thus the mild laxative action may continue for several days, which may explain partially the growing popularity. The drugs may also be used to color alkaline solutions. Isacen is a synthetic resembling phenolphthalein in action.

Large single doses of phenolphthalein seem to be remarkably safe, but continued use of smaller amounts frequently leads to diarrhea, serious skin eruptions, and collapse. On this account, the many proprietary remedies of the drug, which are so highly advertised, are to be strongly condemned.

Phenolsulfonphthalein is used as a test of kidney function; it is excreted mainly by this channel, a small amount by the bile. One cubic centimeter of a solution containing 6 milligrams is injected intramuscularly or intravenously ½ hour after preliminary administration of about 400 cc. of water to insure free urinary secretion. The bladder is emptied just before injection, and afterward the urine is allowed to drain into a vessel containing one drop of 25 per cent sodium hydroxide. At the end of 2 hours the collected urine is diluted to 1 liter and compared in color with a standard. The total quantity excreted should amount to 75 per cent of that administered, and the degree of functioning can be calculated by the proportionate amount excreted within 2 hours.

Iodophthalein and its bromine analogue in the form of sodium salts, are employed as carriers of halogen, because they appear in the gall bladder in sufficient amounts to cast a shadow to the X-ray. The salts are injected in 2 portions ½ hour apart before breakfast time, the meal being omitted. The isomeric phenoltetraiodophthalein sodium (iso-iodeikon) is claimed to be better because of smaller dose and because functioning of the liver can be determined by the same dose.

Phenoltetrachlorphthalein is excreted almost entirely by the bile and can be used, therefore, as a test of liver functioning. It is injected by vein in the form of its sodium salt, and the amount in the feces determined; or the amount in the duodenum can be collected by tube; or the time of disappearance from the blood may be ascertained.

Bromsulphalein is injected intravenously for the same purpose, the disappearance from the blood stream being an indication of functional activity of the liver.

6. Iris

Blue Flag (Iris Versicolor), N.F. The dried rhizome of *Iris versicolor*, or of *I. Caroliniana* (*Iridaceæ*). Dose: 2 Gm., 30 grains.

Orris (Iris Root, Orris Root), N.F. The peeled and dried rhizome of *Iris florentina*, *I. germanica*, or *I. pallida* (*Iridaceæ*).

No active principles have as yet been isolated from these drugs. They are infrequently prescribed as cathartics and are also said to be emetic and diuretic. Orris is added to tooth powders, and its oil is highly prized in perfumery.

DRASTICS

The drastics, or hydragogues, are drugs containing resinous substances which are probably very closely allied and which require the presence of bile for dissolving them. In small doses they cause evacuation quite rapidly but are highly irritating, giving considerable colic. The stools are more or less watery from what appears to be effusion into the intestines but to a large extent due to water retention. Unlike the emodin drugs, the action takes place throughout the whole tract. In larger doses all of them may cause acute enteritis sufficient to endanger life. They are employed particularly in dropsical conditions, usually with carminatives to prevent griping. In very small amounts, podophyllum may be used as a laxative, but the others seem to bring about constipation.

1. Podophyllum

Podophyllum (May Apple, Mandrake), U.S.P., B.P. The dried rhizome and roots of *P. peltatum* (*Berberidaceæ*).

Resin of Podophyllum (Podophyllin), U.S.P., B.P. Dose: 0.01 Gm., 1/6 grain, U.S.P.; maximum 1 grain.

Indian Podophyllum, B.P. From *P. emodi.* Used in India.

Podophyllum was a gift from the American Indians. It contains two isomeric resins, podophyllotoxin and the less powerful picropodophyllin, which are characterized by their slowness of action, usually 10 to 12 hours or more. In small doses, the drug is much used as a laxative for chronic constipation, since there seems little tendency for it to bring on this condition, as do other drastics. In larger amounts it is a powerful substance, 0.5 gram having been fatal in one case. Podophyllotoxin is very irritant to the skin and mucous membranes, especially of the eye. It is efficient as a purgative after hypodermic injection but is very irritating locally, with the tendency to form abscesses, and may produce severe nephritis. Like many other purgatives, podophyllum is credited as a cholagogue, although modern experimentation has thrown great doubts on this belief.

2. Jalap

Jalap, N.F., B.P. The dried tuberous root of *Exogonium Jalapa* (*Convolvulaceæ*). Dose: 1 Gm., 15 grains, N.F.; maximum 20 grains.

Resin of Jalap, N.F. Dose: 0.125 Gm., 2 grains.

Compound Powder of Jalap, N.F., B.P. Dose: 2 Gm., 30 grains, N.F.

Tincture of Jalap, N.F. Dose: 4 cc., 1 fluidrachm.

Fluidextract of Jalap, N.F. Dose: 1 cc., 15 minims.

Powdered Jalap, B.P.

Ipomea (Orizaba Jalap Root, Mexican Scammony Root), N.F., B.P. The dried root of *Ipomœa orizabensis* (*Convolvulaceæ*). Dose: 0.125 Gm., 2 grains, N.F.

Resin of Ipomea (Scammony Resin, B.P.), N.F. Dose: 0.2 Gm., 3 grains.

Jalap is the mildest, least disagreeable, and one of the most popular drastics. It will generally produce a profuse, watery stool in 2 to 4 hours after administration. The active components are several resinous glucosides, especially convolvulin, which are active in the presence of bile. The amount of intestinal irritation is a minimum. Larger doses are powerful, giving considerable colic and several liquid movements. Some claim that jalap may be used in chronic constipation, but it is usually limited to dropsies, as an aid to anthelmintics or combined with other purgatives. Mixtures with calomel are said to lack the usual griping. The drugs obtained from various species of *Ipomoea* and of *Convolvulus* are similar in composition and application.

3. Colocynth

Colocynth (Bitter Apple, Colocynth Pulp), N.F., B.P. The dried pulp of the unripe but fully-grown fruit of *Citrullus Colocynthis* (*Cucurbitaceæ*). Dose: 0.125 Gm., 2 grains, N.F.; maximum 5 grains.

Extract of Colocynth, N.F. Dose: 0.03 Gm., ½ grain, N.F.; maximum 2 grains.

Compound Extract of Colocynth, N.F., B.P. Dose: 0.25 Gm., 4 grains, N.F.

Pill of Colocynth and Hyoscyamus, B.P.

Compound Pills of Colocynth and Jalap (Vegetable Cathartic Pills), N.F.

Colocynth was formerly much employed as a drastic and as an adjuvant to other purgatives. The chief components are an alkaloid and several resins, which strongly irritate the intestinal walls, giving hyperemia and often severe inflammation. A dose of 4 grams is said to have been fatal, and 1 gram may be dangerously toxic. It is partially excreted in urine and milk, so that it is contraindicated with nursing mothers. Hypodermic administration gives the purgative action but cannot be used because of the accompanying nephritis. Colocynth is also administered with colchicum in gout.

4. Croton Oil

Croton Oil (Oleum Tiglii), N.F. The fixed oil expressed from the seeds of *Croton Tiglium* (*Euphorbiaceæ*). Dose: 0.06 cc., 1 minim; maximum 2 minims.

Croton oil, which is one of the most *powerful purgatives,* owes its properties to a resin, which is destroyed by boiling and is diluted by the neutral fat. One drop causes a burning in the mouth and stomach, sometimes vomiting, much pain in the abdomen, and, after an hour or two, repeated stools, which are first hard then watery. Large doses lead to fatal collapse, 20 drops being usually sufficient to cause death. Externally, the oil causes hyperemia and pustulation.

Croton oil is rightly *employed* very little, being limited to very obstinate cases of constipation, such as that from lead poisoning, and to unconscious or insane patients. Its use as a counter-irritant is dangerous and has been abandoned. It has been applied in dilute olive-oil solution as a local stimulant to the scalp.

The *treatment of poisoning* would be evacuation, demulcents, and symptomatic remedies.

5. Euonymus

Euonymus (Wahoo Bark), N.F. The dried bark of the root of *Evonymus atropurpureus* (*Celastraceæ*). Dose: 0.5 Gm., 8 grains.

Fluidextract of Euonymus, N.F. Dose: 0.5 cc., 8 minims.

Wahoo bark was introduced into medicine as a drastic purgative for dropsical conditions. It has been found to contain several amorphous, bitter principles, some of which have a digitalis action on the heart. Because of its local irritation and nauseant effects, it is not usually recommended, although occasionally prescribed in respiratory disease as purgative, expectorant, and diaphoretic.

6. Bryony

Bryonia (Bryony Root), N.F. The dried root of *Bryonia alba* or of *B. dioica* (*Cucurbitaceæ*). Dose: 1 Gm., 15 grains.

Tincture of Bryonia, N.F. Dose: 4 cc., 1 fluidrachm.

Bryonia is similar to colocynth and elaterin. It is more powerful when fresh and also when collected in the fall. It has been used by the homeopath in pneumonia. Elaterin, from the fruit of *Ecballium Elaterium*, is effective in very small doses, that formerly recommended in the pharmacopœia being 0.003 gram.

7. Gamboge

Gamboge (Cambogia), N.F. The gum resin obtained from *Garcinia Hanburyi* (*Guttiferæ*). Dose: 0.125 Gm., 2 grains; cattle, 15 Gm., ½ ounce.

Gamboge, which resembles colocynth somewhat, is not irritant as such, but in the presence of bile and fat it becomes powerfully purgative. This action is attributable to cambogic acid, which even in small doses causes repeated, thin stools. Gamboge is now seldom used except in combination, as in compound pills of calomel or in proprietary remedies. Amounts as low as 4 grams have proved fatal.

Other Purgatives

Hundreds of other drugs are purgative, and many of these are so used. The chief objection to the majority is that they also irritate the upper tract to cause nausea and vomiting. Of the substances commonly applied as salines, the citrates, tartrates, and acetates might be mentioned. The emollients act by lubrication; petrolatum, olive oil, and linseed are often so applied. Honey, lactose, and saccharine fruits are mildly laxative, as are also charcoal, yeast, and sulfur. Many irritants, especially the alteratives like baptisia, guaiac, sarsaparilla, and stillingia, probably depend upon purgation for their reputation. In addition, the mercurials (calomel) are important members of the group. The common use of bran or roughage in the diet for the purpose of stimulating movement of the bowel is not without its dangers and should not be practiced except with the advice of a physician.

In cases where the muscular tone of the intestines is weak, especially after operation, the administration of *stimulating remedies* might improve the chronic constipation. Strychnine, pituitary, eserine, or choline derivatives are sometimes applied to this purpose, but drug therapy under such conditions needs more study.

ANTIDIARRHEICS

The drugs used for checking defecations are either local agents or act upon the peripheral or central nervous system. Of the latter class, the opiates are most important, while atropine and its allies are also employed. The astringents and demulcents, lime water, bismuth, tannic acid drugs, and calcium salts are used locally. A diet of raw apples in children seems effective.

CHOLAGOGUES

The term cholagogue was given years ago to those purgatives which increased biliary flow but has since been extended to include any substance which will accomplish this result. Cathartics give bowel movements which are darker in color, suggesting more bile, but this has been shown to be because the food residues are hurried through the tract without giving any chance for bile absorption and for decomposition of the pigments. It is now known that none of the purgatives have any stimulant effect upon the liver or increases the output in any way. In fact they defeat this purpose to some extent by preventing absorption of bile salts, which are the only true cholagogues. Investigations have demonstrated that oxgall is somewhat effective and that possibly salicylates and olive oil have some influence. Calomel is said to be clinically effective, although experiments do not substantiate this claim. In the past, hundreds of substances have been described as cholagogues, but today very few are actually prescribed for this purpose. The present list includes bile salts, calomel, salicylates, podophyllum, olive oil, rhubarb, phosphates, aloe, and aqua regia. As a matter of fact, there is probably never any clinical need for a cholagogue, since so-called biliousness is generally not due to deficiency, and drugs could seldom succeed in remedying obstructed bile ducts.

1. Oxgall

Oxgall, U.S.P. The fresh bile of the ox, *Bos taurus* (*Bovidæ*).

Extract of Oxgall, U.S.P., B.P. Dose: 0.4 Gm., 6 grains, U.S.P.; maximum 10 grains.

Bile Salts, N.R. Dose: ½ to 2 grains per day.

Glycotauro, N.R. Concentrated ox bile freed from pigments and regulated to contain 50 per cent of the bile salts.

Decholin (Dehydrocholic Acid), N.R. An oxidation product of bile acids.

Decholin Sodium, N.R.

Bile, which has a disagreeable, bitter taste, has no *action* when given by mouth, except a mild purgation. It does not interfere materially with gastric digestion and apparently aids the lipases of the intestine in the solution of fats. The chief components of bile are cholesterin, pigments, sodium taurocholate, and sodium glycocholate. The two last are absorbed, collected in the liver, and reexcreted by the biliary duct, while the pigments are decomposed. The salts stimulate the liver to increased bile production because the increase in both liquids and solids seems to be somewhat larger than can be accounted for by the dose given. In this respect the taurocholate is more active. The natural bile is thought to exert some antiseptic action, since, in biliary obstruction, the stools are subject to more putrefaction, but part of the explanation may well rest in the decreased movement. Presence of bile seems to be necessary for the action of some purgatives, notably the drastics. Injected directly into the blood stream, bile brings about striking alterations in normal functions, including depression of the central nervous system, circulatory collapse, and hemolysis of the corpuscles, by lowering surface tension. In this property it resembles the saponins.

Oxgall formerly had a high reputation as a bitter tonic, for local application to wounds and ulcers, and for local injection in snake-bite. It is also sometimes given by enema as a laxative but is not superior to soaps and similar substances, which are more easily available. The main value in therapeutics is considered to be a cholagogue, for which purpose it is without a rival. As has already been stated, however, the indications for such an action are far from being clear, and the efficiency of bile is not high. The attempt to overcome an obstruction in the bile duct is of doubtful wisdom, for it is difficult to imagine that a small increase in bile could forcibly eject the calculi.

Decholin and its salt, besides being used as are the other preparations of bile, have been recommended as detoxifiers in pneumonia, urticaria, arsenic poisoning, etc. The value is considered doubtful.

2. Leptandra

Leptandra (Culver's Root), N.F. The dried rhizome and roots of *Veronica virginica* (*Scrophulariaceæ*). Dose: 1 Gm., 15 grains.

Extract of Leptandra, N.F. Dose: 0.25 Gm., 4 grains.

Fluidextract of Leptandra, N.F. Dose: 1 cc., 15 minims.

The fresh root is a purgative and an emetic, while older specimens are much milder. In fact many say that they are physiologically inert. The eclectics consider leptandra an excellent cholagogue, without intestinal irritation, and prescribe it in place of calomel.

STOMACHICS

The stomachics are a class of drugs which have little in common except a bitter taste. They are very old drugs, having been used since ancient times, originally with the idea that the taste indicated an action in some other way, but, in the light of recent knowledge, are now known to be inactive. Quite a large number of them are called alteratives, and we might just as well add to the present list such substances as sarsaparilla which are to be described later.

The stomachics, or bitter tonics, are agents which *increase* the *appetite* and the *secretion* of digestive juices. They do this only in cases of disfunction, as in cachexia, anemia, etc., and can be expected to have no effect upon the normal individual. Other physiological actions are unimportant, even if the drug is taken into the blood stream. If they are introduced into the stomach by some means other than by mouth, they are ineffective, showing that the benefits are purely psychological reflexes set up by the odor and taste.

They are *used* in convalescence; anemia; where the gastric juice is deficient; and in other digestive disorders; also as anti-emetics, to disguise more disagreeable tastes; and by enema as anthelmintics for threadworms. Overdoses may produce nausea and thus directly defeat the primary purpose. The bitters are administered in liquid or powder form, usually blended, sometimes in pills and tablets which are obviously illogical. Since the effect is desired at mealtimes, the drugs are best given 15 to 30 minutes beforehand. They are often said to be antipyretic, a mistaken impression derived from ancient times.

The group is *classified* as (1) simple bitters, which contain neutral principles of generally not well-understood constitution; (2) astringent bitters, whose ingredients are accompanied by tannin; (3) aromatic bitters, which contain volatile oils and do not mix well with water. The condiments in ordinary use are stomachics which represent the transition to the carminatives.

Simple Bitters

1. Gentian

Gentian, U.S.P., B.P. The dried rhizome and roots of *Gentiana lutea (Gentianaceæ).* Dose: 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Compound Tincture of Gentian, U.S.P., B.P. Dose: 4 cc., 1 fluidrachm, U.S.P.

Extract of Gentian, N.F., B.P. Dose: 0.5 Gm., 8 grains, N.F.

Fluidextract of Gentian, N.F. Dose: 1 cc., 15 minims.

Compound Infusion of Gentian, N.F., B.P. Dose: 15 cc., 4 fluidrachms, N.F.

Concentrated Compound Infusion of Gentian, B.P.
Elixir of Gentian, N.F.
Elixir of Gentian and Iron, N.F. Dose: 4 cc., 1 fluidrachm.
Glycerinated Elixir of Gentian, N.F.

Gentian is the most useful and widely used of all bitters because it is most agreeable. It contains a crystalline glucoside, gentiin or gentiopicrin; and an amorphous principle, gentiamarin.

2. Taraxacum

Taraxacum (Dandelion Root), N.F. The dried rhizome and roots of *Leontodon Taraxacum* (*Compositæ*). Dose: 4 Gm., 1 drachm.
Fluidextract of Taraxacum, N.F. Dose: 4 cc., 1 fluidrachm.
Extract of Taraxacum, N.F. Dose: 1 Gm., 15 grains.
Compound Elixir of Taraxacum, N.F.

Dandelion root is mildly laxative and bitter. It formerly had wide popularity as diuretic, cholagogue, and alterative but is now only occasionally employed in atonic dyspepsia with chronic constipation. Any virtues it may have can be ascribed to its bitter taste and laxative action.

3. Calumba

Calumba (Columbo), N.F., B.P. The dried root of *Jateorrhiza palmata* (*Menispermaceæ*). Dose: 1 Gm., 15 grains, N.F.
Tincture of Calumba, N.F., B.P. Dose: 4 cc., 1 fluidrachm, N.F.
Fluidextract of Calumba, N.F. Dose: 1 cc., 15 minims.
Infusion of Calumba, B.P. (Fresh and Concentrated.)

Calumba contains at least three alkaloids, a neutral and bitter principle, and some mucilage. It is sometimes used in atonic conditions of the alimentary tract, in diarrhea to remove flatulence, and rarely in intestinal tuberculosis. Like quassia, it can be injected by rectum for threadworms.

4. Quassia

Quassia (Bitter-wood), N.F., B.P. The wood of *Picrasma excelsa,* known in commerce as Jamaica Quassia, or of *Q. amara,* known in commerce as Surinam Quassia (*Simarubiaceæ*). Dose: 0.5 Gm., 8 grains, N.F.
Tincture of Quassia, N.F., B.P. Dose: 2 cc., 30 minims, N.F.
Infusion of Quassia, B.P. (Fresh and Concentrated.)
Fluidextract of Quassia, N.F. Dose: 0.5 cc., 8 minims.

Quassia contains several bitter substances called quassins and no tannins. The drug is used as a simple bitter in combination, as an anthelmintic enema for threadworms, and as an insecticide in agriculture. It has also been recommended in chewing gum as a substitute for the smoking of tobacco.

5. Berberis

Berberis (Oregon Grape Root), N.F. The dried rhizome and roots of species of the section *Mahonia* of the genus *Berberis* (*Berberidaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Berberis, N.F. Dose: 2 cc., 30 minims.

The chief component, an alkaloid berberine, is bitter but physiologically very feeble. Berberis and its preparations have been employed in malaria, syphilis, scrofula, and liver diseases, as alterative and cholagogue, but probably have little medicinal value except a stomachic effect.

ASTRINGENT BITTERS

1. Cimicifuga

Cimicifuga (Black Cohosh, Black Snakeroot, Macrotys), N.F. The dried rhizome and roots of *C. racemosa* (*Ranunculaceæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Cimicifuga, N.F. Dose: 1 cc., 15 minims.

Tincture of Cimicifuga, N.F. Dose: 4 cc., 1 fluidrachm.

Like many of the other bitters, cimicifuga has been credited with a great many virtues, some of which still survive. It was considered a useful remedy in chorea, chronic rheumatism, urticaria, neuralgia, deafness, and dysmenorrhea and is still largely employed, in combination with other drugs, for spasmodic conditions of the uterus. In large doses it produces giddiness, headache, and general relaxation, but the amounts used in medicine probably have no material effect. It is presumably no better than any bitter tonic.

2. Condurango

Condurango, N.F. The dried bark of *Marsdenia C.* (*Asclepiadaceæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Condurango, N.F. Dose: 4 cc., 1 fluidrachm.

This drug was once a reputed cure for cancer and chronic syphilis, a view which modern science has discredited. It is still official in many European pharmacopœias, although it probably has only the virtues of any stomachic.

AROMATIC BITTERS

1. Chionanthus

Chionanthus (Fringe Tree Bark), N.F. The dried bark of the root of *C. virginica* (*Oleaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Chionanthus, N.F. Dose: 2 cc., 30 minims.

It has been administered as aromatic bitter, mild laxative, and diuretic.

2. Matricaria

Matricaria (German Chamomile), N.F. The dried flower-head of *M. Chamomilla* (*Compositæ*). Dose: 15 Gm., 4 drachms.

German chamomile is an aromatic bitter rarely used in this country but considered in Europe as an antispasmodic and an anthelmintic. In very large doses it is an emetic.

3. Serpentaria

Serpentaria (Virginia or Texas Snakeroot, Serpentary), U.S.P., B.P. The dried rhizome and roots of *Aristolochia Serpentaria,* or of *A. reticulata* (*Aristolochiaceæ*). Dose: 1 Gm., 15 grains, U.S.P.

Fluidextract of Serpentaria, N.F. Dose: 1 cc., 15 minims.

Tincture of Serpentaria, N.F. Dose: 4 cc., 1 fluidrachm.

Serpentaria is employed as an aromatic bitter in combination with other drugs and occasionally as an adjuvant to antimalarials. Large doses cause symptoms of gastro-enteritis and nephritis.

4. Calamus

Calamus (Sweet Flag), N.F. The peeled, dried rhizome of *Acorus C.* (*Araceæ*). Dose: 3 Gm., 45 grains.

Other Stomachics

It would be impossible to give a complete list here of those substances which have been applied as stomachics. All of the common spices or condiments act in that way. They are usually aromatic. The acids, including vinegar, belong in the same group. Aloe, nux vomica, strychnine, cinchona, quinine, cascara, ipecac, salicin, alstonia, hydrastis and caffeine are applicable and used as simple bitters; orange, lemon, the mints, eucalyptus, asarum, arnica, and zedoary, as aromatic bitters; iron and tannin drugs, as astringent bitters. Arsenic is presumed to play the role of stomachic, as are also alcoholic beverages, bile, and salt. Formerly official were chirata, centaury, coptis, zedoary, cornus, canella, galangal, inula, angelica, and chamomile.

Ginseng, the root of *Panax quinquefolius*, and angostura, the bark of *Cusparia febrifuga*, are still used considerably in folk medicine.

CARMINATIVES

The carminatives are drugs which counteract flatulence and colic. All of them contain volatile oils or other aromatics and have a warm, pungent taste. They exert a mildly irritant action upon the stomach, decreasing peristalsis but in the intestine increase movement somewhat. Their efficiency in lessening the discomfort from gas, the colic of purgatives, and other abdominal pains and in similar claimed effects is unexplained. The possibility of attributing them to motor stimulation, to antiseptic or reflex effects, is not to be overlooked, for they are often very effective therapeutically. The most popular are mints, capsicum, ginger, and pepper, although almost any aromatic, including some of the bitters and all volatile oils, should be effective.

1. Peppermint

Peppermint, U.S.P. The dried leaves and tops of *Mentha piperita* (*Labiatæ*). Dose: 4 Gm., 60 grains.

Oil of Peppermint, U.S.P., B.P. Dose: 0.1 cc., 1½ minims, U.S.P.

Peppermint Water, U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.

Concentrated Peppermint Water, B.P.

Spirit of Peppermint, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.

Menthol, U.S.P., B.P. An alcohol, $C_{10}H_{19}OH$, obtained from oil of peppermint or other mint oils or prepared synthetically. Dose: 0.06 Gm., 1 grain, U.S.P.

Camphorated Menthol, N.F.

Compound Ointment of Menthol, N.F.

Compound Spray of Menthol, N.F.

Oil of peppermint, because of its menthol, is a very popular carminative, flavor, stomachic, and domestic diuretic. Menthol is applied locally as a rubefacient and local sedative in the same way as camphor, in itching skin diseases, in the nose, in neuralgia, and in headache. It may also be somewhat antiseptic. Hypodermically, its effects are identical with those of camphor.

2. Capsicum

Capsicum (Cayenne Pepper, African Chillies), U.S.P., B.P. The dried ripe fruit of *C. frutescens* (*Solanaceæ*). Dose: 0.06 Gm., 1 grain, U.S.P.

Tincture of Capsicum, U.S.P., B.P. Dose: 0.5 cc., 8 minims, U.S.P.

Oleoresin of Capsicum, N.F. Dose: 0.015 Gm., ¼ grain, N.F.; maximum 1 grain.

Ointment of Capsicum, N.F., B.P.

Tincture of Capsicum and Myrrh (Hot Drops, Thomsonian Number Six), N.F. Dose: 2 cc., 30 minims.

Capsicum depends for its action upon a neutral substance capsicin or capsaicin, which has a very pungent and lasting taste. It is employed as stomachic and carminative, especially to supply local effects in alcoholic cases. The powerful irritation, without vesication, from local application is also utilized as a counter-irritant in various conditions and as a stimulant in alopecia and throat afflictions. Since it is excreted by the kidneys, capsicum has been recommended as a diuretic and aphrodisiac, but results from this method have been very doubtful.

3. Ginger

Ginger (Zingiber), U.S.P., B.P. The dried rhizome of *Zingiber officinale* (*Zingiberaceæ*) with outer cortical layers removed, known in commerce as Jamaica Ginger. Dose: 0.6 Gm., 10 grains, U.S.P.

Oleoresin of Ginger, N.F. Dose: 0.03 Gm., ½ grain.

Tincture of Ginger, B.P.

Strong Tincture of Ginger, B.P.

Syrup of Ginger, N.F., B.P. Dose: 10 cc., 2½ fluidrachms, N.F.

Fluidextract of Ginger, U.S.P. Dose: 0.6 cc., 10 minims.

Ginger is very popular as a flavor, stomachic, and carminative. It has also enjoyed a considerable reputation among the laity as a diaphoretic emmenagogue but is probably not superior to other volatile oils. It is an agreeable addition to purgatives in preventing griping and is also sometimes used to produce counter-irritation.

4. Myrrh

Myrrh, U.S.P., B.P. A gum resin obtained from *Commiphora Abyssinica* or from other species of *C.* (*Burseraceæ*).

Tincture of Myrrh, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Myrrh is one of the oldest of medicaments, and to this may be attributed much of its former, now waning, popularity. It was used by the Egyptians for embalming and as an incense. Today it is administered with purgatives for its carminative action; with stimulating expectorants in bronchitis; applied locally on ulcers and in the mouth in stomatitis or pharyngitis, in order to produce local stimulant or astringent action. It is a component of some dental powders. Myrrh has an extraordinarily persistent reputation for affections of the uterus, such as amenorrhea, but probably without foundation.

5. Spearmint

Spearmint (Mentha Viridis), U.S.P. The dried leaves and tops of *Mentha spicata* (*Labiatæ*). Dose: 4 Gm., 60 grains.

Oil of Spearmint, U.S.P. Dose: 0.1 cc., 1½ minims.

Spearmint Water, U.S.P. Dose: 15 cc., 4 fluidrachms.

Spirit of Spearmint, U.S.P. Dose: 1 cc., 15 minims.

Solution of Soda and Mint (Mixture of Soda and Mint, Soda Mint), N.F. Dose: 8 cc., 2 fluidrachms.

Spearmint, although much different in composition, is employed in the same way as peppermint, being probably less useful. Its oil contains carvone which has the action of other volatile oils.

6. Asarum

Asarum (Canada Snakeroot, Wild Ginger), N.F. The dried rhizome and roots of *A. canadense* (*Aristolochiaceæ*). Dose: 2 Gm., 30 grains.

Compound Syrup of Asarum, N.F.

This drug is very similar to ginger in medicinal properties but milder. It is employed for stomachic and carminative action in about the same way. The volatile oil has been used largely in perfumery.

7. Ethyl Acetate

Ethyl Acetate (Acetic Ether, Acetic Ester), N.F. $C_2H_5OOC{\cdot}CH_3$. Dose: 1 cc., 15 minims.

Ethyl acetate is comparable with ether in its physiological action but less volatile and less active. It is employed as a flavor, carminative, aromatic stimulant, and antispasmodic by inhalation. Occasionally, it is applied by inunction in rheumatic pains.

Other Carminatives

Many drugs depend upon a volatile oil for carminative properties; among the more important are anise, fennel, caraway, turpentine, and juniper. Malodorous substances, such as asafetida, valerian, and sumbul, are often applied in this way. Of the numerous other drugs given for the purpose, we might mention ether, ammonia, camphor, chloroform, spirit of nitrous ether, charcoal, arnica, pepper, calumba, and xanthoxylum.

DIGESTANTS

At least *two factors* are necessary for normal digestion, namely, a certain hydrogen ion concentration and the hydrolytic enzymes. In the stomach these are secured by pepsin and hydrochloric acid; in the intestines, by several enzymes and alkalinity.

The **enzymes** are colloidal materials of unknown composition, probably protein in nature. They act best at about body temperature with a narrow range of hydrogen ion concentration and are often much affected by the presence of foreign substances. In the dry state they can be preserved for some time but in solution are rapidly decomposed, especially at somewhat elevated temperatures and immediately upon boiling. Excessive acidity or alkalinity, antiseptics, alcohol, protein precipitants, and many salts prevent their activity and may destroy them. Pepsin can be rapidly decomposed in solution by shaking in the presence of air, while pancreatin, even in the dry state, is quite unstable. Pepsin will completely decompose the latter in weakly acid solution, although in the presence of slight alkalinity the reverse takes place, and the pepsin is destroyed.

The enzymes have been widely *used* to aid in digestion in conditions of supposed deficiency. Administration by mouth can be expected to accomplish this purpose only in the case of pepsin or if the other enzymes are protected from action in the stomach. Mixtures of enzymes are entirely illogical, although they are often used. Since the digestive juices and enzymes are not often lacking, much of this form of treatment could be discarded. Furthermore, it is difficult to administer the enzymes so as to get any activity. A more logical field would be to predigest food, and this is frequently utilized. They may also be employed to digest excessive or necrosed tissue. Pancreatin is sometimes applied to get rid of necrotic bone, and pepsin has been used on the false membrane of diphtheria.

In the *stomach* the *acidity* is maintained normally by hydrochloric acid in the strength of 0.2 to 1 per cent, usually 0.4 to 0.5. Such amounts not only furnish a suitable medium for peptic digestion but also assist in regulating the sojourn of food. In cases of deficiency, therefore, the administration of hydrochloric acid, or of any other acid, will supply the necessary amount. Excessive quantities delay food discharge and inactivate the enzymes. Acids also aid chemically in digesting connective tissue, are more or less antiseptic in the stomach and upper bowel, and tend to increase somewhat the secretion of enzymes in the intestine. Excessive amounts interfere with most digestive processes and, hence, with metabolism. These are facts illogically used in the treatment of obesity. Since the normal acid of the body is hydrochloric, this is the agent of choice where deficiency occurs, but any of the other mineral acids would probably accomplish the purpose as well.

In general, the acids may be *used* to assist in rendering the urine acid by drawing on the alkaline reserve, largely diluted as refreshing drinks in fever, and to bring about stomachic effects. They are also applied locally as styptics and astringents or anhydrotics. Their employment as cholagogues is without foundation, as is also the claim for lithontriptic value, although the dissolving of phosphate calculi is a possibility if the acidity can be sufficiently raised. In cases of urate stones, this method might be actually harmful. On the basis that alkalosis is either a cause or a constant accompaniment of allergy, acids have been recommended as remedies.

1. Hydrochloric Acid

Hydrochloric Acid, U.S.P., B.P. An aqueous solution containing not less than 35 per cent and not more than 37 per cent of HCl.

Diluted Hydrochloric Acid, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.; maximum 60 minims.

Betaine Hydrochloride (Acidol), N.R. $C_5H_{11}NO_2{\cdot}HCl$. Dose: 0.5 Gm.

Hydrochloric acid is used as described in the preceding discussion and also as a counter-irritant in sciatica, when painted along the nerve. It is an antiseptic in very low concentrations, by some claimed to be more effective than hypochlorites, and has the advantage of stimulating growth of new tissue. Injections of very dilute solutions have been used for all types of infections, but the method may be dangerous, and the evidence for great benefits is lacking. Betaine hydrochloride was introduced to avoid the irritating effect of free acid and to permit administration in the dry form. It is decomposed by water to the inert alkaloid and hydrochloric acid.

2. Nitrohydrochloric Acid

Nitrohydrochloric Acid (Nitromuriatic Acid, Aqua Regia), N.F. A concentrated aqueous solution containing hydrochloric acid, nitric acid, nitrosyl chloride, and chlorine. Dose: 0.2 cc., 3 minims.

Diluted Nitrohydrochloric Acid, N.F. Dose: 1 cc., 15 minims.

Besides being useful like other acids without any advantage over them, nitrohydrochloric acid has had a notable reputation as cholagogue and in the treatment of diseases of the liver. The content of chlorine makes it a powerful antiseptic. It is the acid most often employed in allergies (hay-fever).

3. Phosphoric Acid

Phosphoric Acid, U.S.P., B.P. Not less than 85 per cent and not more than 88 per cent of H_3PO_4.

Diluted Phosphoric Acid, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.

Phosphoric acid is especially popular in refrigerant drinks and with sodium phosphate to make the urine acid. Formerly it was often administered in nervous diseases, as were all phosphorus compounds.

4. Sulfuric Acid

Sulfuric Acid, U.S.P., B.P. Not less than 94 per cent and not more than 98 per cent of H_2SO_4.

Diluted Sulfuric Acid, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 60 minims.

Aromatic Sulfuric Acid (Elixir of Vitriol), U.S.P. Dose: 0.5 cc., 8 minims; maximum 20 minims.

Sulfuric acid is used as has been described in general for the acids and occasionally as a powerful caustic. The aromatic preparation, which is often given in lead poisoning, contains ethyl sulfuric acid which has the properties of other mineral acids.

Any of the *strong acids* (hydrochloric, phosphoric, sulfuric, nitric, glacial acetic, etc.) will cause *fatal poisoning* if in sufficient concentration. The symptoms after swallowing the liquids are those of gastro-enteritis, namely, a burning sensation in the mouth, throat, and esophagus, nausea, vomiting, abdominal pain, diarrhea, and blood often in the excretions. The stronger acids also leave corroded spots on the clothes and skin, and this may amount to perforation of the walls in the alimentary tract. Secondary effects, which rapidly follow, are cold sweat, muscular weakness, feeble pulse, and respiratory collapse. The first step in treatment is to neutralize the acid with a non-corrosive alkali if possible, magnesia, chalk, soap, or soda being preferred in the order given. Evacuation may be performed, although this is hardly necessary and, if the alimentary walls are greatly corroded, may be dangerous. Demulcents, plenty of water, and stimulants complete the treatment.

5. Pepsin

Pepsin, U.S.P., B.P. A substance containing a proteolytic enzyme obtained from the glandular layer of the fresh stomach of the hog, *Sus scrofa* var. *domesticus* (*Suidæ*). Dose: 0.5 Gm., 8 grains, U.S.P.

Glycerite of Pepsin, N.F. Dose: 2 cc., 30 minims.

Elixir of Pepsin, N.F. Dose: 8 cc., 2 fluidrachms.

Compound Elixir of Pepsin (Compound Digestive Elixir), N.F. Dose: 8 cc., 2 fluidrachms.

Elixir of Pepsin and Bismuth, N.F. Dose: 8 cc., 2 fluidrachms.

Elixir of Pepsin, Bismuth and Strychnine, N.F. Dose: 8 cc., 2 fluidrachms.

Elixir of Pepsin and Rennin (Essence of Pepsin), N.F. Dose: 8 cc., 2 fluidrachms.

Saccharated Pepsin, N.F. Dose: 1 Gm., 15 grains.

Enzymol, N.R. An extract prepared from the fresh animal stomach.

Rennin (Rennet), N.F. The partially purified milk-curdling enzyme obtained from the glandular layer of the stomach of the calf, *Bos taurus* (*Bovidæ*).

Pepsin is used under conditions of deficient amounts of gastric juice or of the enzyme. As a matter of fact, there is seldom any such lack, and, when there is, it is the acid which is needed. In those rare cases in which the secretions of the *stomach,* sufficiently acidified, will not digest proteins, pepsin may be of value, but it is certainly useless, even if harmless, in the vast majority of instances in which it is used. It is usually administered during or after meals. Many of the pepsin preparations are probably almost inert, because the enzyme is very unstable under a variety of conditions. A much more logical use of pepsin is in the preparation of predigested foods and rarely for the softening of dead tissue or for the solution of false membranes. The pepsin elixirs, including essence of pepsin, are probably valueless, except as vehicles. The subcutaneous or intramuscular injection of sterilized pepsin is claimed by some as an almost specific means of curing gastro-duodenal ulcer.

Enzymol is designed as an application to old sores, ulcers, and slow-healing wounds. It is claimed to correct offensive odors, to exert a solvent action on pus and sloughing and necrotic tissue, and to impart a healing stimulus.

Rennin has the power to coagulate the casein of milk and is used for that purpose solely, being sold commercially as "junket tablets."

6. Pancreatin

Pancreatin, U.S.P., B.P. A substance containing enzymes, principally amylopsin, trypsin, and steapsin, obtained from the fresh pancreas of the hog, *Sus scrofa* var. *domesticus* (*Suidæ*), or of the ox, *Bos taurus* (*Bovidæ*). Dose: 0.5 Gm., 8 grains, U.S.P.

Compound Pancreatin Powder (Peptonizing Powder), N.F.

Trypsin, N.R. The proteolytic enzyme of the pancreas largely separated from the other constituents. Dose: 0.125 Gm. or more three times a day.

The pancreatic enzymes may be divided into *three classes* represented by trypsin, which digests protein; amylopsin, which hydrolyzes starches and sugars; and steapsin, which digests fats. The last is so unstable that it is practically absent from all preparations or from the official pancreatin. In aqueous solution the entire activity sometimes disappears in 24 hours.

Trypsin acts in slightly alkaline media, not exceeding 1 per cent of sodium bicarbonate, at a temperature of 40°C. It is a very unstable substance, especially in aqueous solution, but is more stable in alcohol or glycerin. The commercial preparations usually contain so little that their proteolytic power is negligible.

Amylopsin, the carbohydrate enzyme, is the most stable of the pancreatic enzymes. It acts best at about 40°C. in weakly alkaline media; even weak acid solutions inhibit the action or destroy it.

The only enzyme practically available in pancreatin is amylopsin, and, for this reason, there is little therapeutic indication. Malt diastase would be as efficient. Furthermore, if the material is not protected in the stomach, all of it will be destroyed. The diagnosis of pancreatic deficiency is almost impossible under usual conditions, and there is seldom such a positive indication. Sometimes pancreatin is used to predigest food, but malt and pepsin would seem adequate. The use of the former or any of its enzymes to destroy tumors has not given much satisfaction.

7. Malt

Extract of Malt (Maltine), U.S.P., B.P. A product obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of *Hordeum vulgare* (*Gramineæ*).

Malt and its extract may be used for flavoring or as foods. The amylotic enzyme, diastase, which was formerly official, may be employed to predigest foods, as in breakfast cereals.

Other Enzymes

Several vegetable materials contain enzymes which have been recommended and used in medicine. Probably the best known in the **diastase** of malt, which was formerly official, but whose commercial preparations are often of little activity. **Taka-diastase,** from *Eurotium oryzæ,* a Japanese mold, is used in a similar way but is less efficient and unreliable. **Papaya** (*Carica papaya*) fruit contains a tryptic ferment, **papain,** which was suggested as a substitute for pepsin because it will act in either weakly acid or weakly alkaline solution. It has been frequently prescribed but later experimentation has shown that its efficacy is doubtful and certainly variable.

NUTRIENTS

The nutrients, or medicinal foods, are those substances used to supply special needs in the dietary of the sick. They can furnish nothing more in the way of alimentation than can be expected of the usual foods for normal individuals, notwithstanding exaggerated claims made for some of the commercial preparations. For certain special purposes they supply a definite need, as in diets for diabetes, predigested foods for patients who are poorly equipped for normal digestion, and material wholly absorbable for those whose alimentary mucous membranes are unhealthy.

It is impossible to consider in this volume all phases of medicinal foods. In the treatment of disease the physician must, of course, give serious thought to diet and often prescribes given articles of food, either natural or artificial. This has led to the introduction of a host of commercial nutrients which are manufactured substances designed for use under special conditions. Thus, there are some for diabetics, some to be used only in heart disease, some as adjuvants to convalescence from fevers, etc. The great majority furnish simple calorific requirements of a particular sort and, as has already been noted, can accomplish nothing more in the diet than usual foods for normal persons, although they may do this in a special way or in exaggerated proportion. Of this class, which is strictly nutritional, only the official articles will be mentioned.

In calculating the value of a medicinal food, several factors must be considered. The *nutritional value* in calories can easily be estimated by analysis, the customary heat units being used for each gram of fat, carbohydrate, and protein. Such figures, while given a great deal of importance by many, do not supply any real basis for comparison, because it is well known that the three primary food constituents do not always behave in the same way when subjected to the digestive processes. Furthermore, many other substances may have value in nutrition. The *digestibility* and *palatability* must be carefully considered, as also the qualitative character of the *products of hydrolysis*. The ultimate compounds from proteins differ greatly in value to metabolism, as do also to a lesser extent those from the polysaccharides. The **mineral salts,** too, probably merit more study than is usually accorded them, since some of the essential elements are more valuable than others. Finally the question of **vitamins** must be considered carefully, not only in disease, but also when there is no noticeable evidence of illness.

1. Milk Products

Cow's Milk (Lac Vaccinum), N.F. The pasteurized or unpasteurized milk of the domestic cow, *Bos taurus* (*Bovidæ*), without modification.

Bacillus Acidophilus Milk, N.R. Whole milk cultured with *B. acidophilus.* Dose: 1 liter a day.

The nutritive value of milk and its products needs no special comment. The powdered preparations are equally effective. For the treatment of certain dietary disorders of children, the reduction in carbohydrates of milk and increase in proteins is presumed to be indicated. In some cases lactic acid is added, or the milk is cultured by organisms. Other preparations are designed for similar purposes, especially the separated casein or its calcium combination.

The various *cultures* of lactic acid organisms, and soured milk prepared by means of them, were introduced in an attempt to replace pathogenic bacteria in the intestinal tract by those which are harmless. Metchnikoff expressed the theory that it should be possible to drive out the harmful bacteria by administering an indifferent one in enormous amounts. The one he finally selected was *B. bulgaricus*, much used by Europeans to sour milk. The evidence apparently shows that this organism cannot be made to grow in the alimentary tract but that the normal *B. acidophilus* can be increased by massive administration. Consequently, cultures of the latter have recently become quite prominent. It has been shown, however, that these cultures gradually lose their power to grow in the intestinal canal after they have been cultivated for some time outside the body, so that only recently isolated cultures are of value in therapy.

Artificially or naturally soured milks are possibly of value for other purposes, particularly for children. They are used in diarrhea, certain types of vomiting, and certain other forms of digestive disturbances, apparently with uniform benefits. The reason for such advantage is not clear.

2. Meat Products

Extract of Beef, N.F. The residue obtained from beef broth by evaporation at a low temperature.

Elixir of Beef and Iron, N.F. Dose: 8 cc., 2 fluidrachms.

Meat extracts have little food value but are used by the laity, under the impression that they represent a concentration of the original meat used in their manufacture. Extract of beef may be employed, for the small amount of nutriment that it contains in feeding infants, invalids, and convalescents, where it serves the additional purpose of stomachic tonic. The mixture with iron is designed to increase the appetite and promote digestion, as well as furnish iron for the blood.

Other Nutrients

All of the sugars, including honey and caramel, and starch are common articles of diet which could be applied in medicinal feeding. Some of the emollients are often useful in the same way. Olive oil, linseed meal, almond, and cocoa butter are the most important. The demulcents, like acacia, tragacanth, elm, chondrus, and althea, have generally very low food value, but some of them, notably gelatin, fig, and prune, are common. In addition, the alimentary qualities of alcohol, yeast, and glycerin should be noted.

VITAMINS

The great importance of these factors in metabolism was recognized only after 1920, but the amount of literature since that time has been tremendously voluminous. The name "vitamine" was given in 1911 to a factor in yeast whose lack in the diet was found to produce polyneuritis. Some time later this and other factors which had been noted were designated by letters, and the final "e" was eliminated to give "vitamin" as a general name for such requisite substances in foods.

At present writing (1937) six of these vitamins are well recognized; a seventh has recently been fairly characterized; and an eighth and others are suspected or doubtful. Although the letters are still employed for most of them, the chemical identity of some has led to the use of coined names. The story of isolation and investigation of each is an intensely interesting one, but space does not permit its telling. All six of the recognized vitamins have been separated in the purified state, and three or four of these have been synthesized, one (C) being now a marketed article.

1. Vitamin A

Carotene, N.R.
Carotene in Oil, N.R.

Vitamin A, or substances which are changed to it, is found in the fatty portions of many natural foods but particularly in marine liver oils (halibut, cod, etc.). When any such sources are lacking in the diet, a definite disease results, characterized by night blindness (xerophthalmia in animals), loss of appetite and weight, edema, and colitis. There is also good evidence that susceptibility to infection is one sequel, although administration of the vitamin in infections is ineffective as a remedy.

At least four natural substances are transformed in the body to vitamin A, probably by the liver. They are alpha, beta, and gamma carotene, $C_{40}H_{56}$, crystalline substances closely allied to the terpenes and found widely in vegetables, and cryptoxanthine. Betacarotene, which is much the most active and also the most common, can give the same effects as A, although it is less readily absorbed. The vitamin itself has recently been synthesized, thus establishing its constitution, $C_{20}H_{30}O$.

The administration of foods containing A or carotene is employed to treat conditions in which it is lacking; under such circumstances it may be said to be specific. As an aid in preventing infections, A seems effective only when the disease has been caused or threatens to be caused by previous deficiencies. Certainly A has not been demonstrated to prevent generally colds, influenza, pneumonia, etc. Other claims for carotene and A, such as prophylaxis against renal calculi and securing of growth in children, have not been proved. The effective dose is 20,000 to 60,000 units (1 unit = 0.0006 mg. of pure betacarotene).

2. Vitamin B_1 (B, F)

This antineuritic factor has had the longest history. It was probably first recognized as early as 1897, although it was not studied until more than fifteen years later. It is found very widely in the water-soluble part of many plants, such as corn, wheat, soy bean, and green vegetables, but the principal sources are yeast and the outer coating of rice. Associated with it in yeast and rice are B_2 and perhaps other factors (Bios, B_3, B_6, H, Y, etc.), which were originally grouped as B. Vitamin B_1 has been isolated in the pure state, and its constitution as a pyrimidine derivative ($C_{12}H_{16}ON_4S$) of a thiazole has been established by synthesis.

Deficiency of B_1 brings about a condition of polyneuritis or beriberi. If the lack is not great, there appear to be many changes in the nervous system, endocrines, the intestines, etc., as well as a possible susceptibility to infection.

The allowable claims for therapeutic value are comparatively few. Whenever there is a deficiency, of course, administration is called for, but determinations of this lack are often difficult. Preparations are used in loss of appetite, subnormal growth, beriberi, and in some conditions in which there is trouble in administering ordinary bulky foods. Applications in numerous other ways which have been recommended on experimental grounds are as yet unproved. Among these are hyperthyroidism, intestinal atony, neuritis of unknown origin, diabetes, infections, and ulcerative processes. The effective dose is considered to be 50 to 200 international units (1 unit = 10 mg. of absorption product from rice polishings).

Yeast Extract, N.R. 25 units of B_1 and 10 units of B_2

Yeast, which is a rich source of several vitamins, was employed in medicine on empirical grounds many years ago. It was called an alterative and used in cases of boils and various skin diseases, also applied locally to burns and wounds. Aside from its content of vitamins and a mild, uncertain catharsis, it is probably useless. In cases of rare, proved deficiency in B_1 and B_2, however, there is little question of the value of yeast. Indiscriminate recommendation to the laity for any purpose must be severely condemned, since these vitamins are rarely lacking in the diet, and more harm than good may easily result.

3. Vitamin B_2 (G)

In the original B it became increasingly evident during the period up to 1930 that there are several essential factors. At least one of these, B_2 or G, has now been separated in the more or less pure condition and found to belong to the flavin group. There is also some evidence for the existence of other vitamins in the old B complex, but, at the present writing, universal recognition for these is lacking.

It is possible that several of the flavins will be found effective as vitamin B_2, but today we have proof only for a substance known as lactoflavin or riboflavin. This is a yellowish, water-soluble substance found quite widely in natural foods but usually in smaller amounts than B_1. Yeast, rice polishings, milk, eggs, and liver are especially good sources. Its quantity is commonly determined on ability to secure growth in test animals. Knowledge of deficiency symptoms and of therapeutic indications is yet decidedly incomplete, although the disease pellagra is presumed to be closely related. Except as a supply when there is a demonstrated or supposed lack in the diet, riboflavin is not yet called for in medicine.

4. Vitamin C

Cevitamic Acid (Ascorbic Acid, Vitamin C, Cebione), N.R. Laevo-$\mathrm{CH_2OH{\cdot}CHOH{\cdot}CHO{\cdot}COH{:}COH{\cdot}CO}$. Dose: protective in infants ⅙ grain, corresponding to 15 to 30 cc. of fresh orange juice.

This factor was originally separated from the adrenal glands of animals and has since been found in many other natural substances. Citrus fruits, paprika, tomatoes, and cabbages are particularly rich sources. It is also prepared synthetically from one of several sugars. Since it is very readily oxidized in the air and light, it must be preserved carefully, best in ampuls.

Deficiency of vitamin C brings on the disease scurvy, which can be prevented or cured by adequate dosage of the crystalline material or of foods containing it. Symptoms of scurvy are chiefly peripheral hemorrhages, fragility of bones, loosening of teeth, and general malaise.

Therapeutically vitamin C promises to become very valuable. The only claim which is clearly recognized is for the cure or prevention of scurvy, whether this be definitely evident or entirely subclinical. Under such circumstances, administration of cevitamic acid is strictly specific. However, there are an increasing number of reports to show value in conditions which, although often accompaniments of scurvy, have not been caused by the latter. Among these conditions might be mentioned dental caries, pyorrhea, loss of appetite, anemia, various infections, hemorrhages, skin diseases, leukemia, colitis, diabetes, rheumatism, diphtheria, tuberculosis, and anaphylaxis. Up to the present writing it is impossible to evaluate administration of C for such purposes, but it is safe to say that ultimately the acid will be found of great aid in the treatment of some of these conditions.

5. Vitamin D

Cod Liver Oil, U.S.P., B.P. The partially destearinated, fixed oil obtained from fresh livers of *Gadus morrhua* and of other species of the family *Gadidæ.* Dose: infants 4 cc., 1 fluidrachm; adults 8 cc., 2 fluidrachms, U.S.P.

Non-destearinated Cod Liver Oil, U.S.P.

Emulsion of Cod Liver Oil, U.S.P. Dose: infants 8 cc., 2 fluidrachms; adults 15 cc., 4 fluidrachms.

Emulsion of Cod Liver Oil with Hypophosphites, N.F. Dose: 15 cc., 4 fluidrachms.

Emulsion of Cod Liver Oil with Malt, N.F., B.P. Dose: 15 cc., 4 fluidrachms, N.F.

Emulsion of Cod Liver Oil with Egg, N.F. Dose: 15 cc., 4 fluidrachms.

Cod Liver Oil Concentrate, N.R. Dose: 10 to 40 drops daily.

Tablets of Cod Liver Oil Concentrate, N.R.

Oscodal Tablets, N.R. A preparation of the non-saponifiable fraction. Dose: 10 to 60 mg. three times a day.

Carotene with Vitamin D Concentrate, N.R.

Solution of Irradiated Ergosterol (Viosterol), U.S.P., B.P. Dose: 0.3 cc., 5 minims, prophylactic daily for infant, U.S.P.

Cod Liver Oil with Viosterol, N.R. Not less than 850 units of A and 360 units of D per gram. Dose: 2.5 to 7 cc. or more.

Sodium Morrhuate, N.R. The sodium salt of the unsaturated fatty acids of cod liver oil.

Halibut Liver Oil (Haliver Oil), N.R. A fixed oil obtained from the fresh livers of *Hippoglossus hippoglossus.* Not less than 44,800 units of A and 540 units of D per gram. Dose: 6 to 20 drops daily.

Halibut Liver Oil with Viosterol, N.R. Not less than 9000 units of D per gram. Dose: 8 to 20 drops daily.

Burbot Liver Oil, N.R. Extracted from livers of the burbot, *Lota maculosa (Gadidæ).* Not less than 4480 units of A and 640 units of D per gram. Dose: 16 minims a day.

Percomorph Liver Oil, N.R. A mixture containing oils from fresh livers of percomorph fish and 50 per cent of cod liver oil. Not less than 60,000 units of A and 8500 of D per gram. Dose: 10 to 20 drops daily.

Vitamin D is a term applied to one or more sterols which are found in the marine liver oils or are prepared by irradiation of fatty substances by ultraviolet. Whether or not these are identical chemically is yet undecided but also not important if the therapeutic results are similar. The story of how this vitamin was traced from the early beginning with cod liver oil to a substance obtained from ergosterol by irradiation is one of the most thrilling in pharmaceutical history, but limitations of space preclude a retelling. Substances giving effects attributed to D can be found in the oils and can be manufactured by exposing to ultraviolet or sunlight of certain sterols, whether purified or in solution. Even exposure of the animal body to such irradiation will give results similar to those from administration of substances containing the vitamin. One of the compounds obtained from ergosterol by ultraviolet treatment has been separated in high purity and named calciferol (D_2), $C_{28}H_{43}OH$.

The principal function of D is apparently to regulate metabolism of calcium and phosphorus, either directly or through the endocrine system. Absence of it in the diet invariably leads in children to rickets or diseases closely allied, spasmophilia and osteomalacia. With varying degrees of thoroughness, each of the mentioned sources of D will prevent or cure these diseases, but complications often render the administration more or less ineffective. There is also much evidence for the use of D in prophylaxis or cure of dental caries, infantile tetany, tendency to bleeding, infectious diseases, chronic ulcers, tuberculosis, hay fever, postoperative tetany, etc. In each case any benefits are attributed to improved metabolism of calcium or phosphorus.

The discussion of vitamin D would not be complete without mentioning irradiation of foods. Any food which contains requisite sterols can be made more or less antirachitic by such a process, a fact which has given rise to the Steenbock patent. It is particularly employed in the production of vitamin D milk by irradiation. Other means of arriving at antirachitic milk are by feeding irradiated yeast to the cow or by adding viosterol to the commercial milk. All three methods apparently give a product which is effective, although they differ much in efficiency.

Cod liver oil was used by the Norwegians years before its peculiar value was known to medicine. The crude livers were placed in barrels and allowed to putrefy partially, when the oil separated and was drained off. The disagreeable character of this oil has since been obviated by modern scientific methods, so that the product used today is practically free from disagreeable features and yet possesses all of the virtues which could be assigned to the older oil.

It is very easily emulsified and absorbed, even from the intact skin. In small doses it *acts* as a food, since a tablespoonful gives about 120 calories in an easily assimilable form. In larger amounts there may be distaste, disagreeable eructations, nausea, diarrhea, and disturbances of digestion. These may be eliminated in large part by beginning with small quantities and gradually increasing or by employing some of the commercial, flavored emulsions. Like all fats, it is better tolerated in cold weather.

The oil is *used* as prophylactic and curative in rickets, also in xerophthalmia and keratomalacia, the results being eminently satisfactory. It has been employed in various forms of malnutrition in childhood, in wasting diseases like tuberculosis, scrofula, and chronic bronchitis, and generally in all cases of impaired nutrition and debility. Various skin diseases are presumed to be alleviated by the drug given orally, generally administered about 2 hours after meals, or by inunction.

The *value* of cod liver oil was originally referred to its content of alkaloids (from putrefaction), of phosphorus, of iodine, or of bromine. Later, after modern methods removed these without lessening the therapeutic worth, its efficacy was attributed to availability as a food, due to the peculiar unsaturated acids, jecoleic and therapic acids. We now refer its success to the vitamins, A and D, since the latter especially is found in the oil to a greater extent than in most other substances.

Halibut liver oil has a much higher amount of both A and D and is used for the same purposes. Cod liver oil contains at least 600 units of A and 85 units of D per gram, while halibut liver oil has about 45,000 and 540 units respectively. Percomorph and burbot oils are designed to be used in the same way.

Sodium morrhuate is employed in about 5 per cent solution as a sclerosing agent.

6. Vitamin E (X)

This factor, the antisterility vitamin, which was discovered in 1922, is found in many natural foods, such as green vegetables and particularly the germ cells of wheat. It has recently been separated and purified and found to be an alcohol, $C_{29}H_{50}O_2$, to which has been given the name of "tocopherol."

Absence of this factor from the diet of animals makes them unable to reproduce, and there is no reason to suppose that this does not also apply to human beings. The wide occurrence of the vitamin in nature and in common foods, however, precludes any danger of deficiencies, and up to the present this renders any therapeutic application unimportant. Studies now under way may ultimately indicate a useful role in the treatment of certain diseases of the reproductive system.

7. Vitamin K

It seems to have been well proved that foods contain an antihemorrhagic factor which has been termed K. This is found richly in alfalfa. From animal experiments it would appear to function through mobilization of the enzyme, prothrombin. Therapeutic applications are at present writing not much studied, but a few reports indicate the uselessness of K in hemophilia.

THE GENITO-URINARY TRACT

Diuretics

The diuretics are substances that increase the amount of urine excreted. This may be accomplished in a variety of ways, because of the complicated structure of the kidneys and because of their susceptibility to foreign influences. As a matter of fact, it is difficult to state positively in what manner a given diuretic acts, and in many cases the effect may have been gained by a combination of conditions. In general, however, *diuresis* is brought about by (1) changes in the circulation; (2) osmosis or salt action; or (3) local stimulation of the renal structure.

An *alteration in circulation* which would cause a greater output of urine may consist of general vasoconstriction with minimum effect in the kidneys or of increased heart action with a consequent rise in blood pressure. In either case the large amount of blood flowing through the organ will result in an augmented excretion, which is roughly proportional to the glomerular tension. In this way digitalis and its allies, which increase the amplitude of the heart-beats, are efficient diuretics, if the circulation is previously in any way impaired, and if the dose is large enough.

The administration of any solid which can be carried in the blood stream will increase the excretion of urine by *salt action.* Any large excess of fluid in circulation will accomplish the same effect. Lowered osmotic pressure expands the blood vessels, increases the glomerular pressure, and probably also gives reabsorption from the tubules. Any soluble material will be effective in this manner, but in practice water, salts, milk, sugars, or other harmless substances are most often employed. Of the inorganic salts, those of potassium are considered best, combined with the anions chloride, nitrate, or iodide. The bromides, because of their cerebral action, are not so useful. In general it may be said that the diuresis by any salt is inversely proportional to its diffusibility. Thus a carbonate is more active than a citrate, and potassium more so than sodium.

The third class of diuretics, those which *stimulate locally*, contains a large number of drugs whose action is little understood. The majority are known to be irritants to mucous membranes and especially to the renal structure, where they are supposed to cause some dilation of the glomeruli and possibly also to stimulate the functional activity of the filtration cells. Any irritant will, in moderate amount, produce an increased output of urine, but excessive doses compress the tubules and injure the cells, with a consequent anuria and often albuminuria. The essential oils, alcohol, glucosides, cantharides, acids, mercury (merbaphen), etc., probably act as diuretics by such irritation.

The **purin group** of alkaloids, although not irritant, is presumed to belong in this class. The mechanism of their diuretic action is very little understood, in spite of the fact that they are considered efficient and have been studied frequently. Caffeine itself, because of prominent action upon the nervous system, is little used as a diuretic, but theobromine and theophylline are often employed for this purpose. The effect may be due partly to dilation of the kidney arterioles, partly to salt action, and even to direct effect upon the secretory nerve ends.

Diuretics are *indicated* in relatively few conditions and never when the urinary output has been lessened by disease of the kidneys. Dropsical states of cardiac origin or those which are caused by alteration in the general metabolism are effectively decreased by digitalis or salts. Collection of fluid because of renal insufficiency, however, must be treated in other ways. Whenever the urine is irritating to the passages or contains pus and bacteria or caustic poisons, diuretics will dilute in such a way as to decrease the discomfort. For the same reason, a threatened obstruction in ureter or urethra may be prevented, and it is possible that such a calculus already formed could be removed by this means. Another reason for the administration of diuretics is given as aid in removing toxins from the body. While this may be of value in eliminating saline poisons from the circulation, it is doubtful if the efficiency is high with others. Removal of strychnine, for instance, is but little effected by diuresis. In spite of these few indications, however, drugs of this class are frequently employed and, in more than a few cases, with great advantage.

For most purposes, a *combination* of diuretics seems of optimum character, regardless of the experimental fact that the effect is often merely summation. Thus, caffeine and theobromine merely give a result which would be obtained if the total dose had been of either one. In some cases, however, there may be true synergism. Whether there is or not, opinion seems positive that combinations are advantageous.

1. Water

Water, N.F. Natural water.
Distilled Water, U.S.P., B.P.
Sterilized Distilled Water, U.S.P.
Redistilled Water (Triple- or Double-distilled Water), N.F.
Ampuls of Redistilled Water, N.F.

The principal value of water in any system of therapy is as solvent, diluent, and detergent. Since these are intimately discussed throughout the student's course, it is unnecessary to elaborate on the subject here. The importance of it as a diluting material in digestion, where it plays an important role in increasing the activity of enzymes and digestive fluids, is a therapeutic application of this principle. As a diluent for irritating substances which cause nausea, water may have decided influence as antiemetic.

The employment of water as a *remedial agent* per se is also important, as even a superficial study of therapeutical measures will make evident. In pure form, it is not absorbed by the skin but, because of its hypotonicity, is capable of giving a mild irritation and even softening and swelling. In the form of baths, this may be utilized as a local stimulating measure in certain skin diseases, improving the circulation and nutrition of the epidermis, thereby removing the adverse conditions. Furthermore, the local irritation, especially if the bath is hot, will reflexly stimulate in such a way as to counteract pain, leading to circumstances which promote a normal sleep. The same reflex stimulation from a hot bath, particularly with added irritants, can be employed to reestablish menstruation. It is also said that baths of body temperature are the best remedies in nervous insomnia. In the stomach, hot water in sufficient quantity will cause emesis. Ice applied to small cuts will prove an effective hemostatic because of local vasoconstriction.

Water is rapidly absorbed from mucous membranes in general, but very little or not at all in the stomach. It thereby *increases fluid* in the blood stream, making it hydremic or hypotonic in comparison with other body fluids, and leads to interchange of materials and increased activity of the excretory organs. With sufficient quantities, even the normal bowel movement will be stimulated. Diuresis is one of the most important effects, being prompt, large, and certain when the kidneys are not diseased. Diaphoresis, and to a lesser extent salivation and expectoration, are also enhanced. Abnormal temperature is lowered by sweating and by mechanical heat consumption, so that drinking large amounts of fluid, or cold baths, may be effective antipyretic measures.

All of the results from ingestion of water in quantity combine to increase the elimination of waste matter and even to raise the amount of catabolic products. The *metabolic balance* is altered to an appreciable degree, although not in proportion to the fluid intake. This increased destruction and excretion may be utilized for reduction of obesity and has also been attempted, with little justification, as an alterative measure for a large number of pathological conditions. It is probably true that abnormal fluid intake can induce marked changes in the metabolism which will be of advantage under limited conditions, but the restrictions must also be clearly recognized.

2. Potassium Salts

Potassium Acetate, U.S.P., B.P. $KC_2H_3O_2$. Dose: 1 Gm., 15 grains, U.S.P.

Potassium Chloride, N.F. KCl. Dose: 1 Gm., 15 grains.

Potassium Citrate, U.S.P., B.P. $K_3C_6H_5O_7{\cdot}H_2O$. Dose: 1 Gm., 15 grains, U.S.P.

Effervescent Potassium Citrate, U.S.P. Dose: 4 Gm., 1 drachm.

Solution of Potassium Citrate, N.F. Dose: 15 cc., 4 fluidrachms.

Potassium Nitrate, U.S.P., B.P. KNO_3. Dose: 0.3 Gm., 5 grains, U.S.P.

Potassium is one of the elements essential to life and, as such, is distributed widely in the *human body* and that of other animals. Estimation of the total amount places this at an average of 200 to 300 grams in man. The quantity in any one locality of the body is often in inverse ratio to that of sodium, the former being high in the cells, the latter in the fluids. The average diet adds to the total 2 to 5 grams per day, although this varies considerably because vegetable foods are much richer in potassium than animal foods. There is a corresponding excretion in the same time, chiefly in the urine and feces.

The administration of additional potassium salts by mouth has no other *physiological effect* than those of osmosis and rapid excretion. The diuresis, diaphoresis, and increase of bronchial secretions are higher than those caused by the other alkaline salts and the compounds of ammonium. When given by intravenous injection, however, the large concentration at one time produces a narcotic effect, which is antagonized by sodium in the same way. The necessary amount in the blood, about 1/10,000, is never reached when the salts are given by mouth, unless with enormous doses. The whole central nervous system is depressed, and the muscles are paralyzed directly, especially those of the heart.

Locally, the salts are somewhat irritant to mucous membranes and, if not absorbed quickly after oral administration, may lead to symptoms of *gastro-enteritis.* This is especially true of the nitrate, which has occasionally induced fatal poisoning; 30 grams has been estimated as a lethal dose. Long-continued use of this salt also may give a chain of untoward effects, including fatty degeneration of the heart and tendency to hemorrhages.

All four salts described are *used* as diuretics, diaphoretics, and expectorants, while the citrate and acetate, which are oxidized in the tissues to carbonate, are employed to alkalinize the blood and urine and to combat acidosis. The citrate is also somewhat laxative. As diuretics, the salts are contraindicated in kidney disease, on the basis that non-elimination may lead to poisoning. The possibility of such a condition, however, does not appear to be great. The nitrate is often mixed with stramonium, lobelia, etc., for smoking purposes in asthma, with the idea that it is reduced in the burning to nitrite and can thus exert a relaxing action on the bronchi.

3. Sodium Salts

Sodium Chloride (Salt), U.S.P., B.P. $NaCl$.

Physiological Solution of Sodium Chloride, U.S.P., B.P. 0.85 per cent.

Sodium Acetate, U.S.P. $NaC_2H_3O_2 \cdot 3H_2O$. Dose: 1.5 Gm., 25 grains.

Sodium Citrate, U.S.P., B.P. $Na_3C_6H_5O_7 \cdot 2H_2O$. Dose: 1 Gm., 15 grains, U.S.P.

Solution of Sodium Citrate (Mixture of Sodium Citrate, Potio Riverii), N.F. Dose: 8 cc., 2 fluidrachms.

Ampuls of Sodium Chloride, N.F.

Ampuls of Sodium Citrate, N.F.

While the total amount of sodium in the *animal body* is probably somewhat lower than that of potassium, the major portion is contained in the body fluids and can be varied largely without detriment. With ordinary diets, the income is 10 to 20 grams per day, but large increases over this amount have no apparent effect. Even the administration of sodium salts by intravenous injection produces only osmotic effects, although these can easily be sufficient to cause some poisoning.

Sodium salts are *employed* as diuretics and diaphoretics in the same way as those of potassium, being probably less efficient and not so popular. The citrate, which is an alkalizer like all organic salts, is commonly used in vitro to prevent coagulation of blood; injected intravenously, it appears to shorten the coagulation time, a paradox difficult to explain. It also prevents coagulation when added to the lacteal foods of infants. Sodium chloride is a common condiment, laxative, and emetic (30 grams) and a reflex stimulant when used in the form of salt baths. The citrate is a pleasant, even if mild, laxative. The irritant action of concentrated salt solutions may be utilized as gargle to stimulate growth of epithelial tissue or as antiseptic in throat infections; for such purposes they are often very efficient. Sodium chloride is sometimes employed by enema to combat threadworms and is the best antidote for silver poisoning.

Physiological salt solution is often introduced into the circulatory system to replace blood lost by hemorrhage or by operation, to prevent dehydration in burns, as an aid in remedying uremia, to prevent vomiting in tuberculosis, in sunstroke, and in other conditions. In hypertonic solution sodium chloride is given orally, rectally, or intravenously in simple intestinal obstruction or atony and is injected as a sclerosing agent. Orally it is apparently effective as a treatment of Addison's disease, also in enuresis, hypotension, etc.

Sometimes, as in hypertension, a salt-free diet is deemed advisable. To replace the salt various sodium compounds have been proposed, among them the malate, malonate, gluconate, glutamate, and lactate.

4. Ammonium Salts

Solution of Ammonium Acetate (Spirit of Mindererus), U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.

Solution of Iron and Ammonium Acetate (Basham's Mixture), N.F. Dose: 15 cc., 4 fluidrachms.

Strong Solution of Ammonium Acetate, B.P.

The *physiological effects* of ammonium salts are mostly due to salt action and to the resulting irritation. At the same time, intravenous injection gives respiratory and circulatory stimulation, with slowed pulse, increased blood pressure, and enhanced respiratory rate. Larger doses may lead to medullary convulsions. There also seems to be a curare action on muscles, which is much weaker than with ammonium derivatives like muscarine. The salts are absorbed readily, converted to urea by interaction with alkalies of the blood, and rapidly excreted as such. Normal blood contains but a few milligrams of NH_4 ions per 100 cc., which is intimately concerned with regulation of the hydrogen ion concentration. If acid is high, it is reduced by interaction with the ammonium salt; but if low, the excess alkali combines with the latter. The administration of excess ammonium salts leads to production of the carbonate, thus reducing alkalinity, and the carbonate produced is then converted to urea. The increase in ammonium salt, therefore, tends to produce an acid urine; ammonium chloride is often rated as the best urinary acidifier for methanamine administration and for other purposes.

These salts are *employed* as diuretics, diaphoretics, and expectorants in the same way as potassium and sodium. The chloride is a very common remedy in dry cough or bronchitis, causing the mucus to become thin, an action that is not well understood. It may be due partly to excretion by the bronchi, partly to central stimulation, partly reflex from the irritation of gastro-intestinal lining. The ammonium compounds are also used to increase urinary acidity and that of other fluids and, by intravenous injection, to produce medullary stimulation. The biphosphate is said to be an excellent acidifier. Ammonium mandelate is discussed under the urinary antiseptics.

5. Purine Alkaloids

Caffeine (Theine), U.S.P., B.P. Trimethylxanthine, $C_5H(CH_3)_3O_2N_4 \cdot H_2O$. Dose: 0.2 Gm., 3 grains, U.S.P.; maximum 8 grains.

Citrated Caffeine, U.S.P. Dose: 0.3 Gm., 5 grains.

Tablets of Citrated Caffeine, N.F.

Caffeine with Sodium Benzoate, U.S.P., B.P. A mixture of sodium benzoate and caffeine. Dose: by mouth 0.3 Gm., 5 Grains; hypodermic 0.2 Gm., 3 grains, U.S.P.

Tablets of Caffeine with Sodium Benzoate, N.F.

Ampuls of Caffeine with Sodium Benzoate, N.F.

Caffeine with Sodium Salicylate, N.F. Dose: 0.2 Gm., 3 grains.

Theobromine, N.R. 3,7 Dimethylxanthine, $C_5H_2(CH_3)_2O_2N_4$. Dose: 0.35 to 0.5 Gm., 6 to 8 grains.

Theobromine with Sodium Salicylate, U.S.P., B.P. Dose: 1 Gm., 15 grains, U.S.P.

Theobromine Sodium Acetate (Agurin), N.R. Dose: 0.5 to 1 Gm.

Theocalcin, N.R. A mixture of calcium theobromine and calcium salicylate. Dose: 0.5 to 1 Gm.

Theophylline (Theocin), U.S.P., N.R. 1,3 Dimethylxanthine, $C_5H_2(CH_3)_2O_2N_4$. Dose: 0.25 Gm., 4 grains, U.S.P.

Theophylline with Sodium Acetate (Theocin Sodium Acetate), U.S.P., B.P. Dose: 0.2 Gm., 3 grains, U.S.P.

Theophylline with Ethylenediamine (Aminophylline), U.S.P. Dose: 0.1 Gm., 1½ grains.

Guarana, N.F. A dried paste consisting chiefly of the crushed seed of *Paullinia Cupana* (*Sapindaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Guarana, N.F. Dose: 2 cc., 30 *minims*.

Elixir of Guarana and Celery, N.F. Dose: 8 cc., 2 fluidrachms.

Prepared Cacao (Cocoa), N.F. A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma Cacao* (*Sterculiaceæ*).

Syrup of Prepared Cacao, N.F.

Kola (Cola), N.F. The dried cotyledon of *Cola nitida*, or of other species of *C.* (*Sterculiaceæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Kola, N.F. Dose: 4 cc., 1 fluidrachm.

The three medicinal xanthine derivatives are similar in chemical constitution and in physiological properties. They are all readily absorbed without any great previous action, mostly decomposed in the body to xanthine or its monomethyl compound and excreted in this form and partly unchanged. During this cycle they cause variable and complex effects upon different parts of the organism, both central and peripheral. All three are qualitatively alike but quantitatively very different; theophylline and theobromine are proportionately stronger in peripheral action and lack to a large extent the prominent central stimulation of caffeine, which is a descending one. The chief local effects are diuresis and increased muscular contraction, involving in variable degree almost all muscles.

Caffeine gives a notable stimulation of the *psychic center*. Small doses produce a period of restlessness and increased reflex excitability, which results in an enhanced working power of muscles and a greater capacity for doing work. Thoughts are rendered clearer, sleepiness is banished, and fatigue disappears. Larger amounts cause headache and confusion or even delirium, probably because the succession of ideas becomes complexedly more rapid.

The *respiration* increases notably in rate and depth, especially when poisoning has reduced this materially. The normal breathing is very little affected, and sometimes the action becomes lessened in depth but with a higher amount of total air breathed because of increased rate.

The *muscles*, both striated and unstriated, are stimulated by direct and central action, especially if fatigued. The cardiac muscle and those of the blood vessels are greatly influenced, and rise in blood pressure is aided by an effect upon the accelerator nerve ends. With larger doses, which are not more than therapeutic, this muscular action may be reversed, so that the clinical outcome is sometimes doubtful, if not often so.

The effects upon the *circulatory apparatus*, being a summation of central and peripheral actions, are somewhat complex and usually variable. The vagus is incited, giving a tendency to slow pulse, but the muscular tissue is affected in the opposite way, generally to predominate. With very small doses, the pulse may be slower and stronger than normally, an action which would theoretically be comparable with that of digitalis, if the diastolic relaxation were not absent. The large action on the vasomotor center tends to raise the blood pressure, which is also favored by heightened pulse. While some amounts of caffeine also stimulate the vessel muscles, the usual doses are depressant. The total circulatory change may be assumed to be little or nothing under ordinary conditions, but in cases of poisoning there may be faster pulse and increase in blood pressure.

The *diuresis*, which is very pronounced, is apparently even more complicated and not well understood. It was for years believed that this was entirely due to direct action on the renal epithelium, thus leading to classification as stimulating diuretics. While this is probably partly concerned, other actions are perhaps chiefly responsible for the increased urinary output. The most likely explanation is the increased circulation due to renal vasodilation and to cardiac stimulation. As has already been stated, the muscles of the blood vessels are contracted with small doses and relaxed with larger amounts. The latter effect is noted especially in the kidney vessels, which are often much dilated, even while the others are still contracted and while the blood pressure is normal or slightly high. The net result is a greater glomerular blood supply. In addition, the diuresis may be partly due to other changes induced by these drugs, including direct irritation, inhibition of reabsorption, osmosis, etc.

The *other physiological actions* are relatively unimportant. The temperature is raised in proportion to the dose from 0.5 to 1.2°F. Sometimes mild glycosuria is caused in animals. The products of normal metabolism are also altered in other ways, but this is not of significance during clinical administration.

The *therapeutic uses* of caffeine have already been indicated in part. It is given as an efficient diuretic under conditions of cardiac dropsy and in other circumstances but is usually ineffective or harmful in renal disease. The effect begins promptly after administration, reaches a maximum several days later, and rapidly ceases when the drug is withdrawn. It often fails to act in this way, particularly on a dry diet or after prolonged use. Caffeine is often employed as a circulatory stimulant as is digitalis, chiefly as an adjuvant. Injected hypodermically, it is considered an excellent respiratory stimulant, and it is some times efficient by mouth, but the indications for its use in this way are limited. The psychic effect is utilized in poisoning by morphine and by the other narcotics and also commonly to prevent fatigue and drowsiness. Last, but not least, caffeine is often employed as an analgesic in headache, neuralgia, rheumatic pains, and dyspepsia, being usually given as an adjuvant to acetanilid or other coal-tar anodyne. The explanation of this effect is probably bound up with the psychic effect and with the cerebral vasodilation.

Theophylline and theobromine lack the strong central action of caffeine, but they are more rapid and more effective as diuretics and in action on muscle. Theophylline is the strongest diuretic of the group, but its total effect is usually not desirable, since it may produce gastric disturbances and irritation of the kidneys. Neither of these two can replace caffeine for the central effects and analgesia. The slight solubility of the free bases limits their administration, but this is overcome by the use of the readily soluble mixtures with organic salts.

Theobromine and theophylline are used as diuretics and as cardiac stimulants in heart disease, for the relief of pain in angina pectoris, and for arteriosclerosis and other vascular diseases. In the treatment of various heart ailments, the salt mixtures or theophylline with ethylenediamine are said by some to be almost indispensable.

The *toxicology* of caffeine is not unimportant because, although very large doses can be ingested with quick recovery, even therapeutic amounts may very often cause alarming symptoms. There are excitement, vertigo, sleeplessness, tremors, nausea, diarrhea, frequent urination, palpitation, ringing in the ears, delirium, and sometimes convulsions. The treatment, consisting of evacuation and narcotics, is usually sufficient to bring about recovery. As much as 2 grams has been taken by susceptible individuals without permanent harm.

In this connection it is well to consider the time-honored question of comparative harm from the **caffeine beverages.** Tea contains 2 to 3 per cent, coffee about 1.2 per cent, of this alkaloid, yet a cupful of prepared drink has about a grain in each case, because of the different amounts of material employed. Incidentally, a cup of chocolate or cocoa contains approximately a therapeutic equivalent of theobromine. From the alkaloidal quantity, then, tea and coffee should be equally harmful. It is very doubtful, however, if any untoward results to habitual drinkers can be attributed to caffeine. The effects are: nervousness, insomnia, loss of appetite, emaciation, and digestive disturbances. The tannin of green tea is constipative, and the caffeol of coffee is laxative.

6. Juniper

Oil of Juniper, U.S.P. The volatile oil distilled from the dried ripe fruit of *Juniperus communis* (*Pinaceæ*). Dose: 0.1 cc., 1½ minims.

Juniper (Juniper Berries), N.F. Dose: 4 Gm., 60 grains.

Fluidextract of Juniper, N.F. Dose: 4 cc., 1 fluidrachm.

Oil of juniper berries has had an extraordinary reputation for years as a diuretic and diaphoretic but probably is no more efficient than many other volatile oils, although somewhat more irritant. It is frequently combined with salines and other diuretics and sometimes prescribed as carminative and as antispasmodic in uterine affections. It is to be avoided in the presence of acute or chronic kidney disease.

7. Corn Silk

Zea (Corn Silk), N.F. The fresh styles and stigmas of *Z. Mays* (*Gramineæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Zea, N.F. Dose: 4 cc., 1 fluidrachm.

Corn silk is a mild diuretic, presumed by certain classes of physicians to be very useful in various bladder and urethral diseases and even in gonorrhea. Some have also claimed that it is a cardiac stimulant, but this can reasonably be doubted.

8. Mitchella and Chimaphila

Mitchella (Squaw Vine), N.F. The dried plant of *M. repens* (*Rubiaceæ*). Dose: 2 Gm., 30 grains.

Chimaphila (Pipsissewa), N.F. The dried leaves of *C. umbellata* (*Ericaceæ*). Dose: 2 Gm., 30 grains.

Pipsissewa was used for years by the native American Indians, and later in folk medicine, as an alterative in scrofula and rheumatism, but aside from a mild diuretic and antiseptic action, it is practically useless. Mitchella is similar, with an additional astringency, and is often substituted for chimaphila.

9. Urea

Urea, N.R., B.P. $CO(NH_2)_2$. Dose 0.5 to 4 Gm., 8 to 60 grains, N.R.

It is actively diuretic by osmotic action and practically harmless, being useful in any condition in which a diuretic is indicated, except in renal disease. As an outcome of investigations on maggots, it has been found that urea is an excellent healing agent. The action seems to rest largely on solvent properties, since its bactericidal power is very limited.

10. Hydrangea

Hydrangea (Seven Barks), N.F. The dried rhizome and roots of *H. arborescens* (*Saxifragaceæ*). Dose: 2 Gm., 30 grains.

Elixir of Hydrangea and Lithium, N.F. Dose: 4 cc., 1 fluidrachm.

Fluidextract of Hydrangea, N.F. Dose: 2 cc., 30 minims.

The drug is mildly diuretic and considered by some as a remedy in urinary calculi.

Other Diuretics

Out of the hundreds of drugs that are said to be diuretic, a few might be noted which are used chiefly for other purposes. All volatile oils, or materials containing them, are presumed to be effective. These include turpentine, the mints, anise, horseradish, terpin hydrate, iris, and most of the urinary antiseptics. In addition, the following should be mentioned: cantharides, capsicum, mercury, digitalis, squill, triticum, taraxacum, acids, sweet spirit of nitre, caulophyllum, and eupatorium. Those which are most useful as diuretics have already been named in the preliminary discussion.

URINARY ANTISEPTICS

Disinfection of the urinary tract may be accomplished by local application of antiseptics, or it may be attempted by oral or hypodermic administration. Those bactericidal drugs which are eliminated by the kidneys, or those substances which are decomposed in the body to give similar materials excreted in this channel, are generally referred to as urinary antiseptics. All of them are greatly limited in efficiency by the briefness of contact and the great dilution, but some of them are apparently very selective.

Of the *substances* administered for this purpose, most are volatile oils or oleoresins, and it is often said that almost any oil-containing material will be efficient. Practically, however, the results from this class of drugs have not been very satisfactory, notwithstanding their extended use. The most popular and effective urinary antiseptics are methenamine, mandelates, and urinary acidifiers. Others are hexylresorcinol, buchu, santal oil, copaiba, sabal, methylene blue, benzoates, salicylates, and phenols.

1. Methenamine

Methenamine (Hexamethylenamine, Hexamine, Hexamethylentetramine, Urotropin, Formin), U.S.P., B.P. A condensation product of ammonia and formaldehyde $(CH_2)_6N_4$. Dose: 0.3 Gm., 5 grains, U.S.P.

Ampuls of Methenamine, N.F. Dose: 5 cc. (about 2 Gm.).

Tablets of Methenamine, N.F.

Tablets of Methenamine and Sodium Biphosphate, N.F.

Methenamine is itself *relatively inert* and can be given hypodermically in fairly large doses without causing harmful effects. It is rapidly absorbed and then found everywhere within the body, being finally excreted in nearly all secretions but principally by the urine. Acids decompose it into formaldehyde and ammonium salts, the former then acting as an antiseptic. Since only two fluids of the body, the gastric juice and urine, can generally be acid, only in these liquids can there be any bacterial effect. Occasionally the amount of formaldehyde liberated is sufficient to irritate the mucous membrane.

The drug is *employed* as a urinary antiseptic in various diseases which involve the tract and as a prophylactic before operations. It is sometimes a very satisfactory substance for the purpose, although the amount of formaldehyde liberated is never very large. In order that a maximum effect may be attained, the urine must be made and maintained as strongly acid as possible. This can be accomplished by the administration of sodium biphosphate or a similar agent. In the belief that methenamine is diuretic, it has been given for this purpose for some time, but recent experiments have definitely proved the absence of any effect upon the urinary output.

No benefits could be expected in alkaline fluids, such as the bile and spinal tract, but in spite of this, the drug has often been tried in efforts to make such regions sterile. In addition it has been suggested to stimulate the uterus in labor, to treat the symptoms of alcoholic psychoses, to reinforce the action of antitoxins, with calcium in influenza, etc., but the grounds for so doing are very poorly defined.

The success of methenamine has induced the introduction of numerous salts and other combinations of it, all of which have no advantage whatever. The camphorate, salicylate, borate, etc., may be encountered.

2. Buchu

Buchu (Buchu Leaves), N.F., B.P. The dried leaf of *Barosma betulina* or of *B. crenulata*, known in commerce as Short Buchu; or of *B. serratifolia*, known in commerce as Long Buchu (*Rutaceæ*). Dose: 2 Gm., 30 grains, N.F.

Fluidextract of Buchu, N.F. Dose: 2 cc., 30 minims.

Infusion of Buchu, B.P. (Fresh and concentrated.)

Compound Fluidextract of Buchu, N.F. Dose: 2 cc., 30 minims.

Elixir of Buchu, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Elixir of Buchu, N.F. Dose: 4 cc., 1 fluidrachm.

Elixir of Buchu and Potassium Acetate, N.F. Dose: 4 cc., 1 fluidrachm.

Elixir of Buchu, Juniper and Potassium Acetate, N.F. Dose: 4 cc., 1 fluidrachm.

Buchu is considered to be similar to the other drugs containing volatile oils in tending to make the urine and respiratory passages aseptic. It is used as a diuretic, urinary antiseptic, and expectorant, principally by the laity and by the older school of physicians.

3. Santal Oil

Oil of Santal (Oil of Sandalwood), U.S.P., B.P. The volatile oil distilled with steam from the dried heartwood of *Santalum album* (*Santalaceæ*). Dose: 0.5 cc., 8 minims, U.S.P.; maximum 30 minims.

White Sandalwood, N.F. Dose: 4 Gm., 60 grains.

Santalol (Arrheol), N.R. A sesquiterpene alcohol, the chief constituent of santal oil, $C_{15}H_{26}O$. Dose: 0.4 to 0.6 Gm.

Santyl (Santalyl Salicylate), N.R. Dose: 1.5 cc. a day in four doses.

Oil of Australian Sandalwood, B.P. From *Eucarya spicata.*

Santal oil causes some irritation of the stomach and may disturb the digestion. It is readily absorbed and excreted in the urine, where it exerts some antiseptic action regardless of the hydrogen ion concentration. Sometimes it is distinctly irritating to the urinary mucous membranes, especially of the bladder. Santalol and its esters are claimed to be free from such objections;

beside the salicylate, the carbonate (carbosant) and other esters have been used. Santal oil is also said to stimulate the bronchial secretion and to act as an antiseptic to the respiratory tract, but it is seldom used in that way now.

4. Copaiba

Copaiba (Copaiva, Balsam of Copaiba), U.S.P., B.P. An oleoresin derived from South American species of *Copaiba* (*Leguminosæ*). Dose: 1 cc., 15 minims, U.S.P.; maximum 60 minims.

Copaiba Mixture (Lafayette Mixture), N.F. Dose: 8 cc., 2 fluidrachms.

Copaiba is employed in the same way as santal oil, being a component of several commercial mixtures, and is also said to be diuretic. It has more unpleasant side effects than santal oil and is generally less useful. Both the oleoresin and the oil have been used externally as local stimulants and antiseptics, similarly to balsam of Peru.

5. Sabal

Sabal (Saw Palmetto Berries), N.F. The partially dried, ripe fruit of *Serenoa serrulata* (*Palmæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Sabal, N.F. Dose: 1 cc., 15 minims.

Compound Elixir of Sabal and Sandalwood (Compound Elixir of Saw Palmetto and Sandalwood), N.F. Dose: 4 cc., 1 fluidrachm.

Sabal has been used as diuretic and urinary antiseptic in a way similar to buchu, also as a so-called alterative, expectorant, aphrodisiac, digestant, etc. The evidence as to its efficacy under any of these conditions is very scant, and, aside from possible value as urinary antiseptic, it is probably valueless.

6. Methylene Blue

Methylthionine Chloride (Methylene Blue), U.S.P., B.P. Tetramethylthionine chloride, $C_{16}H_{18}N_3ClS \cdot 3H_2O$. Dose: 0.15 Gm., 2½ grains, U.S.P.

Methylene blue is readily absorbed, distributed through all the tissues, partly reduced, and excreted in the urine and feces which it colors blue. Since part of it is in the reduced state, the blue color of the urine may be increased by oxidizing agents. It may cause slight bladder and intestinal irritation but has usually no untoward effects. It has been used as an analgesic in neuralgia and other nerve diseases, as a urinary antiseptic for various conditions, as a local application in the eye and in skin diseases, and as an intestinal antiseptic in fermentative states and in intestinal tuberculosis. It has been administered in malaria with or without quinine, in leprosy, in pulmonary infections, and as a test for kidney function. For all of these purposes, the drug is more or less of doubtful value and by many considered useless.

Methylene blue was proposed several years ago as an antidote for cyanide poisoning and later in poisoning from carbon monoxide and from acetanilid. It is said to act by forming methemoglobin which produces stable compounds with cyanides. The use for acetanilid has been discredited, but the method in other cases is debated. It is administered by intravenous injection of a 1 per cent solution.

7. Cubeb

Cubeb (Cubebs, Cubeb Fruit), N.F. The dried, nearly full-grown unripe fruit of *Piper Cubeba* (*Piperaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Cubeb, N.F. Dose: 2 cc., 30 minims.

Tincture of Cubeb, N.F. Dose: 8 cc., 2 fluidrachms.

Oleoresin of Cubeb, N.F. Dose: 0.5 Gm., 8 grains.

The volatile oil is somewhat antiseptic and diuretic during excretion in the urine. The drug is recommended for the same conditions as santal oil but is much less useful under the same circumstances and may give rise to very unpleasant side effects. It is sometimes employed as an antiseptic expectorant in bronchitis and as an antispasmodic in asthma. For the latter purpose the drug is smoked in cigarettes, mixed with other drugs acting in a similar manner. In view of the present knowledge of asthma such a procedure is useless as a cure but may give considerable relief.

8. Uva Ursi

Uva Ursi (Bearberry Leaves), N.F. The dried leaf of *Arctostaphylos Uva-ursi* (*Ericaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Uva Ursi, N.F. Dose: 2 cc., 30 minims.

Arbutin, N.R. $C_{12}H_{16}O_7 \cdot \frac{1}{2}H_2O$. A glucoside occurring in uva ursi and many other genera of the family *Ericaceæ.* Dose: 0.2 to 0.5 Gm. three or four times a day.

Uva ursi depends for its effects upon the glucoside, arbutin, which is at least partially hydrolyzed in the body to hydroquinone. The latter is excreted in the urine which, like phenol, it renders smoky. The drug is, therefore, credited with being diuretic and urinary antiseptic, although the evidence for it is very contradictory. It is recommended in various catarrhal conditions of the bladder and urethra.

Mandelic acid and its salts, given orally, have recently become very popular for infections of the urinary tract. The urine must be maintained in a condition higher in acidity than pH 5.5. The results are very favorable to date, although the method may still be considered experimental. By some the mandelates are said to cause some irritation and to be contraindicated in renal insufficiency.

Pyridium (mallophen) and serenium were formerly recommended by the manufacturers for urinary antisepsis, but the first enthusiasm for both has subsided considerably. The former is used in 3-grain doses or locally in dilute solution, while the latter is given orally, 5 grains a day.

Other Urinary Antiseptics

Besides those already mentioned, the list of substances used for this purpose might include most of the irritant diuretics, turpentine oil, terpin hydrate, borates, phenolsulfonates, tar, resorcinol, eucalyptol, gluside, cajuput oil, triticum, balsams of Peru and Tolu, storax, and benzoin, corn silk, thuja oil, and eriodictyon.

URINARY ALKALIZERS AND ACIDIFIERS

The hydrogen ion concentration of the urine may be altered by the administration of substances which have the appropriate reaction, whether or not they are actually eliminated by this channel. The delicate balance maintained by the blood is sensitive to acid or alkaline substances, which draw upon the body fluids and necessitate an excretion to restore the equilibrium. Any harmless substance with the proper reaction will, therefore, be useful for the purpose. The principal acidifiers are ammonium chloride; benzoic, boric, and hydrochloric acids; and primary sodium phosphate. For alkalinization, there may be selected borax, the bicarbonates, lithium carbonate, or the salts of organic acids. Preference is generally given to the last named. These are oxidized within the body to carbonates or bicarbonates and hence accomplish the object desired. The acetates, citrates, salicylates, and benzoates are the agents of choice.

Antilithics and Lithontriptics

The removal of calculi from the urinary canals and also from the biliary duct is very desirable but rather difficult, if not impossible, by the use of drugs. The prevention of formation of these stones is a more hopeful aim and can be accomplished by diet and by diuretic drugs. Substances designed to get rid of them are called lithontriptics; those which inhibit their formation are antilithics. The substances which have been recommended and applied as lithontriptics include olive oil, soda, acids, lithium salts, glycerin, diuretics, and purgatives. The probabilities are that surgery is the only effective method.

The Reproductive Organs

There are many drugs which have been, at one time or another, presumed to increase or decrease the activity of the sexual organs. In any investigations to determine their effects, it is difficult for the scientist to judge of values, because psychological processes are here predominatingly influential. It appears, however, that sexual impotence can best be rectified, if at all, by any system of therapy which will correct deficiencies in general welfare. If the body as a whole is in good normal state, only in exceptional cases should there be need for such remedies. In cases of atonic conditions, fresh air, exercise, and good wholesome food should accomplish the purpose, possibly with the aid of bitter tonics or other substances desired to restore the metabolism to normal.

A drug intended to excite uterine action and restore menstruation is called an *emmenagogue*. If this is for the object of expelling the uterine contents in cases of pregnancy, the drug is termed an *ecbolic* or abortifacient. Fundamentally, there is a difference in the two classes only in degree, the former being but a mild variation of the latter. The stimulation may be brought about by direct action on the uterine muscles or by any irritant which causes reflex effects from congestion. Thus, the purgatives are often prescribed to hasten a delayed menstruation. The most important materials which are assumed to act directly upon the muscular tissue are ergot, pituitary, quinine, and hydrastis, all of which will be described later. Small amounts of any such drug to produce emmenagogue effects are justifiable, but quantities sufficient to cause abortion are invariably dangerous and often fatal.

Those substances which presumably effect an increased sexual desire are called *aphrodisiacs*, while the opposite action is attempted with *anaphrodisiacs*. There are no drugs which are specific for these purposes, and none that will certainly produce the desired effect. Any stimulant to the central nervous system, either directly (caffeine) or reflexly (cantharides), will have a tendency to promote heightened sensibilities; and on the other hand, sedatives (bromides) will blunt them; but the appearance of a positive effect in either case cannot be certain or even probable. The application of endocrine therapy, which gives some promise, will be discussed later.

THE RESPIRATORY TRACT

EXPECTORANTS

Expectorants facilitate expulsion of mucus from the respiratory tract and alter its secretion in a way which favors remedying of bronchial diseases. Several classes of drugs are used in this way, because of the variety of conditions under which they are indicated. A cough is a common accompaniment of many bronchial conditions, since it is a reflex designed by nature to expel foreign bodies or excessive secretion. The term expectorant has come to mean, therefore, any cough remedy.

Expectorants are *used* to increase the fluidity or rate of secretion of mucus, to lessen congestion, to soothe the inflamed surface, to stimulate repair, and to mitigate the conditions which produced the cough reflex, including a bacteriostatic action. In order to be effective, the drug used must be excreted in the respiratory tract, find its way there by inhalation, or have an indirect action upon the center. Of course, if the cough is a symptom only of trouble in some other organ, palliative drugs, such as laxatives and diuretics, may remedy the condition without recourse to expectorants.

The whole group is divided into *three classes:* sedative, stimulating, and anodyne. The first relaxes the vessels and increases secretions and is useful in the early stages of bronchitis, before secretion has begun. It is further separated into the nauseants, which reflexly tend to produce a thin fluid in the air passages; the demulcents; and the salines, which act by osmosis. The stimulating expectorants restore tone to the bronchial muscles, thereby decreasing the amount of mucus, and irritate sufficiently to stimulate growth of new tissue. The anodyne class acts upon the perception and motor nervous centers to inhibit the cough reflex.

There are hundreds of *substances* described in the dispensatories as expectorants, and many of them are commonly used, especially in commercial cough mixtures. The treatment of diseases would undoubtedly be simplified considerably if many of these were eliminated. The most useful are ipecac, tartar emetic, and apomorphine as nauseants; ammonium chloride and carbonate and potassium iodide as salines; terpin hydrate, eucalyptus oil, creosote, and balsams as aromatics; the opiates, chloroform, and hydrocyanic acid as anodynes.

1. Ammonium Chloride

Ammonium Chloride, U.S.P., B.P. NH_4Cl. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Ammonium Chloride, N.F.

Ammonium chloride has the *physiological properties* of other ammonium salts already described under the diuretics. It is rapidly diffused throughout the body, exerting the usual osmotic effects, and in addition makes the urine acid by conversion to urea, setting hydrochloric acid free.

The salt is *employed* like ammonium compounds generally as diuretic, diaphoretic, and central stimulant, but its chief uses are in acute and chronic bronchitis, by inhalation or by mouth, and to render the urine acid. Large doses are emetic. Ammonium chloride is also administered in a large number of other conditions for which there is little evidence, particularly in neuralgia, lumbago, chronic rheumatism, and liver troubles.

2. Tolu Balsam

Tolu Balsam (Tolu), U.S.P., B.P. A balsam obtained from *Toluifera Balsamum* (*Leguminosæ*).

Syrup of Tolu Balsam, U.S.P., B.P. Dose: 10 cc., 2½ fluidrachms, U.S.P.

Tincture of Tolu Balsam, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Like many of the other balsams, Tolu was formerly endowed with great virtues as stimulant and disinfectant expectorant and urinary antiseptic. Its large use in medicine today is chiefly as an agreeable vehicle and adjuvant for cough mixtures.

3. Ipecac

Ipecac (Ipecacuanha), U.S.P., B.P. The dried rhizome and roots of *Cephaelis Ipecacuanha*, known in commerce as Rio or Brazilian Ipecac, or of *C. acuminata*, known in commerce as Cartagena, Nicaragua, or Panama

Ipecac (*Rubiaceæ*). Dose: expectorant 0.06 Gm., 1 grain; emetic 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Powdered Ipecacuanha, B.P.

Fluidextract of Ipecac, U.S.P., B.P. Dose: expectorant 0.06 cc., 1 minim; emetic 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Syrup of Ipecac, U.S.P. Dose: expectorant 0.75 cc., 12 minims; emetic 15 cc., 4 fluidrachms.

Tincture of Ipecac (Wine of Ipecac), N.F., B.P. Dose: 0.6 cc., 10 minims, N.F.

Powder of Ipecac and Opium, U.S.P., B.P. (see Opium).

Emetine Hydrochloride, U.S.P., B.P. The hydrochloride, $C_{30}H_{44}O_4N_2 \cdot 2HCl$, of an alkaloid obtained from ipecac or prepared synthetically. Dose: daily by injection 0.06 Gm., 1 grain, U.S.P.; maximum 1 grain.

Ampuls of Emetine Hydrochloride, N.F. Dose: 1 cc. (about 1 grain).

Emetine Bismuth Iodide, N.R., B.P. Dose: 0.2 Gm. daily, N.R.

Ipecac contains at least *three alkaloids*, emetine, cephæline, and psychotrine, but only the first two are important. These are irritating to mucous membranes, less so to the unbroken skin, and emetic. Emetine, hypodermically, will depress the vasomotor center and the cardiac muscles.

Applied locally, ipecac produces irritation and inflammation, with itching vesicles and pustules which heal rapidly without scar. The powdered drug is very caustic in the eyes, the nasal passages, and the throat, so that workmen must adopt precautionary measures. On the gastric mucosa, there is a similar effect which results in nausea, actual vomiting, and other symptoms of gastro-enteritis. If it is not ejected by emesis, it may cause diarrhea, but there is little or no absorption. Hypodermic injections of the alkaloids produce the same caustic action in the intestine because they are excreted there, also bronchial effects, vasomotor paralysis, and cardiac depression from action of emetine on the muscles. Cephæline is about twice as active by mouth and more toxic than emetine.

The galenicals are occasionally useful for producing *emesis*, since this occurs without dangerous accompaniment, but the action is too slow (½ hour or more) to be important. In smaller doses they are excellent nauseant *expectorants* in the early stages of acute bronchitis. The crude drug is administered in small doses for gouty dyspepsia and other conditions of the alimentary tract, on the basis of irritation of the mucous membrane. It is also considered by some as cholagogue and diaphoretic.

Ipecac was originally introduced in the treatment of *amebic dysentery*, and the careful investigation of this has not altered its reputation; on the contrary, it is considered to be almost specific in any stage. The explanation for the benefits encountered is far from being clear, although we know that the pure alkaloids by the hypodermic route are just as efficacious, and emetine in this way is usually the preference, in order to obviate the nausea. Starting with 0.02 gm. three times a day, the dose is sometimes increased to ten times this amount. Because there is constant danger of poisoning, great care must be exercised; indeed, in the treatment of amebiasis, toxic symptoms are encountered in more than half of the cases, and several fatalities have occurred. The symptoms are rapid pulse, diarrhea, muscular weakness, and polyneuritis, the chief danger being from vasomotor paralysis. Emetine must be classed as a valuable but dangerous remedy in this disease. The total dose in any course of treatment should probably not be over 1 gram. Synthetic remedies for amebiasis, such as chiniofon, acetarsone, carbarsone, and vioform, have been highly recommended, but emetine is usually employed at the start of treatment.

Because pyorrhea was once thought to be caused by an endameba, the local injection of emetine into the gums was tried as a cure, without definite results. The etiology is now considered very doubtful, and certainly emetine is not a cure. It has also been given for other diseases with little success.

4. Terpin Hydrate

Terpin Hydrate, U.S.P. A dihydric alcohol, $C_{10}H_{18}(OH)_2 \cdot H_2O$. Dose: 0.25 Gm., 4 grains, U.S.P.; maximum 20 grains.

Elixir of Terpin Hydrate, N.F. Dose: 4 cc., 1 fluidrachm.

Elixir of Terpin Hydrate and Codeine, N.F. Dose: 4 cc., 1 fluidrachm.

Terebene, U.S.P., B.P. A mixture of terpene hydrocarbons, chiefly dipentene and terpinene, prepared from oil of turpentine. Dose: 0.25 cc., 4 minims, U.S.P.; maximum 20 minims.

Terpin hydrate and terebene are obtained from turpentine oil and are very similar to it in physiological properties. Like other aromatics, they are antiseptic, give diuresis, and stimulate the bronchial mucosa. Terpin hydrate is very popular in this country as an antiseptic expectorant in cough mixtures, or inhaled for the same purpose, and as a diuretic. On account of its agreeableness, it is preferable to turpentine oil for internal medication.

5. White Pine

White Pine (*Pinus Alba*), N.F. The dried inner bark of *Pinus Strobus* (*Pinaceæ*). Dose: 2 Gm., 30 grains.

Compound Syrup of White Pine, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Syrup of White Pine with Morphine, N.F. Dose: 4 cc., 1 fluidrachm.

White pine bark is probably worthless as an expectorant, but its preparations are very popular vehicles for cough mixtures. The compound syrup, with or without morphine, is often prescribed.

6. Senega

Senega (Seneca Snakeroot), N.F., B.P. The dried root of *Polygala S.* (*Polygalaceæ*). Dose: 1 Gm., 15 grains, N.F.

Fluidextract of Senega, N.F., B.P. Dose: 1 cc., 15 minims, N.F.

Syrup of Senega, N.F. Dose: 4 cc., 1 fluidrachm.

Tincture of Senega, B.P.

Infusion of Senega, B.P. (fresh and concentrated).

Senega is a nauseant and, in larger doses, an emetic, owing to at least two substances, senegin and polygalic acid, which are saponins or closely related to them. The diasgreeable taste makes the drug somewhat stomachic, and it is considered a useful expectorant in all stages of bronchitis. It is generally administered as the syrup or in combination with squill in the compound syrup of the latter.

7. Euphorbia

Euphorbia Pilulifera (Pill-bearing Spurge), N.F. The dried plant of *E. pilulifera* (*Euphorbiaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Euphorbia Pilulifera, N.F. Dose: 2 cc., 30 minims.

Compound Elixir of Euphorbia (Antiasthmatic Elixir), N.F. Dose: 4 cc., 1 fluidrachm.

The active principle of this drug has not been isolated. It is used almost entirely as expectorant and antispasmodic in bronchitis and asthma. The fluidextract and a commercial syrup are the preparations generally prescribed, the latter being quite popular.

8. Antimony

Antimony and Potassium Tartrate (Tartrated Antimony, Tartar Emetic, Antimonyl Potassium Tartrate), U.S.P., B.P. $K(SbO)C_4H_4O_6 \cdot \frac{1}{2}H_2O$. Dose: 0.003 Gm., 1/20 grain, U.S.P.; maximum 1 grain.

Compound Syrup of Squill, N.F. Dose: 2 cc., 30 minims.

Tincture of Antimony (Wine of Antimony), N.F. Dose: 1 cc., 15 minims.

Sodium Antimonyl Tartrate, B.P.

Antimony Thioglycollamide, N.R. Dose: 0.08 Gm., by injection.

Antimony Sodium Thioglycollate, N.R. Dose: 0.05 to 0.1 Gm., by injection.

The element antimony was at one time considered very highly in medicine, and numerous compounds were later used as drugs. Beginning with modern scientific medicines, however, it lost more and more of its reputation until today practically the only compound used is tartar emetic.

Because of the acid radicals, some of the compounds are fairly corrosive, but most of them have no effect on the skin or mucous membranes. Tartar emetic is slowly decomposed by the tissues to give salts which are quite irritant, causing *pustulation* and slow-healing abscesses. By mouth, the only physiological action elicited is nausea and *vomiting* by local action and the increase in *bronchial secretions*, sweating, and depression, which usually accompany nausea. If emesis fails to take place, diarrhea follows; but if the vomiting is suppressed by opiates, the main effect is profuse sweating. The systemic actions of antimony, which are best produced by intravenous injection, are exactly like those of arsenic but more severe: cholera-like symptoms, much vomiting, convulsions, collapse, and circulatory failure. The treatment for poisoning from overdoses would be tannin or the arsenic antidote, evacuation, and demulcents.

In therapeutics, tartar emetic is sometimes applied in ointment as counter-irritant and rarely given as an emetic. The principal use, however, is as nauseant expectorant in the early stages of acute bronchitis or in bronchial pneumonia. Organic compounds of antimony have been found efficient treatment for granuloma inguinale, trypanosomiasis, and infestation by flukes (schistosomiasis). They are also used in syphilis and other diseases. The thioglycollamide and thioglycollate are given intramuscularly or intravenously in doses of 1 to 2 grains.

9. Eriodictyon

Eriodictyon (Yerba Santa), U.S.P. The dried leaf of *E. californicum* (*Hydrophyllaceæ*).

Fluidextract of Eriodictyon, U.S.P. Dose: 1 cc., 15 minims.

Aromatic Syrup of Eriodictyon (Corrective Syrup), N.F. Dose: 8 cc., 2 fluidrachms.

Yerba Santa has been employed largely as a stimulating expectorant, stomachic bitter, and urinary antiseptic, for none of which is it very valuable. As a bronchial antispasmodic, it is sometimes mixed with other drugs for smoking. The principal use of the leaves today, however, is to disguise the taste of bitters, a property for which it has a remarkable power. The justification for this is doubtful in the administration of bitters, because the therapeutic value of these is based upon the taste. Other bitter substances are possibly rendered inert by admixture with eriodictyon.

10. Sanguinaria

Sanguinaria (Blood Root), N.F. The dried rhizome and roots of *S. canadensis* (*Papaveraceæ*). Dose: 0.125 Gm., 2 grains.

Fluidextract of Sanguinaria, N.F. Dose: 0.125 cc., 2 minims.

Tincture of Sanguinaria, N.F. Dose: 1 cc., 15 minims.

Sanguinaria is a very irritating and poisonous drug, owing to the alkaloid, sanguinarine, and to several less active bases. The fragmentary investigations of its pharmacological behavior indicate that it is a powerful stimulant, and later depressant, to the spinal cord and medulla, causing convulsions and a marked rise in blood pressure, with subsequent rapid paralysis. The only action used medicinally is the local irritation which occasions nausea and vomiting, indicating it as a nauseant expectorant. It is also sometimes applied locally in skin diseases. The chief preparation for internal medication is the tincture or the eclectic specific.

11. Poplar Buds

Poplar Bud (Populi Gemma, Balm of Gilead Buds), N.F. The air-dried, closed, winter leaf bud of *Populus candicans,* known in commerce as Balm of Gilead Buds, or of *P. balsamifera,* known in commerce as Balsam Poplar Buds (*Salicaceæ*). Dose: 4 Gm., 60 grains.

This drug was once quite frequently used in respiratory, renal, and rheumatic diseases and as a local application in the last. It is now important only as an ingredient of white-pine preparations.

Other Expectorants

Aspidosperma, the dried bark of *A. Quebrachoblanco,* was formerly used in drachm doses in all forms of respiratory disease, not only as nauseant but also to stimulate the medullary centers. It has been called the "digitalis of the lungs." **Cocillana,** the bark of *Guarea Rusbyi,* is a popular remedy in coughs, usually combined with opiates.

Other expectorant drugs are very numerous. Most of those which have not already been mentioned are either salines or irritants. Among the latter might be listed cubeb, buchu, sabal, lobelia, tar, grindelia, benzoates, camphor, myrrh, and oils of turpentine, santal, anise and pine needle.

RESPIRATORY STIMULANTS

Stimulation of the respiration can be produced reflexly by counter-irritants or directly by agents that act upon the medullary centers. Ether, alcohol, acetic acid, ammonia, and camphor are the agents usually employed in the first method, also heat, cold, or friction. The effect is always brief and must be followed by more permanent measures. The centrally acting drugs upon which most reliance is placed are carbon dioxide, caffeine, atropine, strychnine, ammonium salts, cocaine, and cyanides. In emergencies, or as a last resort, it is necessary to perform artificial respiration, which is accomplished by alternately compressing and expanding the lungs by manipulation of the arms or of the chest.

1. Carbon Dioxide

Carbon Dioxide (Carbonic Acid Gas), U.S.P., B.P. CO_2.

This gas, being a product of most combustions and excreted continuously by animals and human beings, is of highest importance to the metabolism. It stimulates the medullary centers if in small concentration and depresses them when in greater amounts, thus acting as a regulator of respiratory and cardiac rates. Should the quantity in the inspired air become higher than normal, the person suffers serious discomfort, actual poisoning, or even death. Three or four per cent may cause some effects, but toxicity is not produced until the concentration has reached 15 to 20 per cent, and air with this amount can be breathed for short periods with impunity, while death follows quickly when the carbon dioxide is in much larger quantity. The symptoms are headache, dizziness, difficulty in breathing, cyanosis, unconsciousness, and other results of asphyxia.

Treatment is extraordinarily effective if the heart still beats. It consists in exposure to pure air and artificial respiration if necessary; generally the symptoms promptly disappear.

The solid form, carbon dioxide snow or dry ice, is caustic by freezing. It is occasionally used to remove freckles or growths or to cause superficial corrosion, but care must be exercised in this process. The common administration of carbonated drinks for digestive disorders, as carminatives and antiemetics, is well known. The gas has also been used as a bath for cardiac and respiratory disorders.

The most important use of carbon dioxide, however, is in its inhalation for stimulation or depression of the medullary centers. For this purpose it is often life-saving and may be considered one of the most valuable of drugs. Whenever the respiration is depressed, small amounts, mixed with oxygen, will usually suffice to remedy, while if there is a spasmodic condition of organs controlled by the medulla, larger doses may counteract it. Carbon dioxide is often employed in pneumonia, influenza, poisoning by carbon monoxide and by depressant alkaloids, during and after anesthesia, in asphyxia of the new-born and threatened death from drowning, and in shock and collapse. Under these conditions it is mixed with 50 to 95 per cent of oxygen and administered by inhalation for a few seconds up to continuously, depending on circumstances. Similar application has been recommended to stimulate the psychic centers in mania, for chronic vasomotor weakness, in acute alcoholism, in uterine inertia in the first stage of labor, to control postpartum hemorrhage, in hypostatic pulmonary congestion, to relieve abdominal distention after laparotomy, etc. Among the spasmodic conditions that have been treated are hiccup, epilepsy, angina pectoris, whooping cough, and bronchial asthma.

2. Cyanides

Oil of Bitter Almond, U.S.P. The volatile oil obtained from the dried ripe kernels of *Amygdalus communis* (*Rosaceæ*), or from other kernels containing amygdalin by maceration with water and subsequent distillation with steam. Dose: 0.03 cc., ½ minim, U.S.P.; maximum 1 minim.

Spirit of Bitter Almond, N.F. Dose: 0.5 cc., 8 minims.

Compound Elixir of Almond, N.F.

Bitter Almond Water, N.F.

Diluted Hydrocyanic Acid, N.F., B.P. About 2 per cent of HCN. Dose: 0.1 cc., 1½ minims, N.F.; maximum 5 minims.

Wild Cherry (Wild Black Cherry Bark, Prunus Virginiana), U.S.P., B.P. The stem bark of *Prunus serotina*, collected in autumn and carefully dried (*Rosaceæ*).

Syrup of Wild Cherry, U.S.P., B.P. Dose: 10 cc., 2½ fluidrachms, U.S.P.

Fluidextract of Wild Cherry, N.F. Dose: 2 cc., 30 minims.

Hydrocyanic acid, or prussic acid, occurs in a number of drugs, usually combined in glucosidal form. The bitter almond contains amygdalin which, upon hydrolysis, yields glucose, benzaldehyde, and hydrogen cyanide, the volatile oil being composed of the last two. Wild-cherry bark and cherry-laurel leaves also give the acid when hydrolyzed. The metal cyanides, but not the complex compounds, give the same physiological action, as does also cyanogen, $(CN)_2$.

The *action* is not exceptionally powerful, since the fatal dose (0.06 gram) of hydrogen cyanide is not relatively low, but the results occur very rapidly, probably because it is so diffusible. There is a brief stimulation of the entire central nervous system, beginning in the medulla and affecting in order chiefly the respiratory, vasomotor, and vagus centers. The heart is slowed, and the blood pressure raised, and the respiration is rendered quicker and deeper. Later the stimulation is replaced by depression, bringing about a fall in pressure and respiratory paralysis, with asphyxia and convulsions. The medullary effects follow so rapidly that it is difficult to determine those on the other parts of the nervous system, but it is probable that they are first stimulated and then paralyzed in the same way, although later. Muscles and nerve endings are also paralyzed, but this is not important in view of the central changes. The explanation of these changes undoubtedly rests in the fact that hydrocyanic acid prevents the liberation of oxygen by oxyhemoglobin; the latter retains its bright-red color even after death. Applied to the skin, cyanides produce numbness by inactivating the nerve tissue.

Cyanides were formerly much *used* for three purposes: to relieve itching in skin diseases by local application, also to mitigate persistent vomiting; to treat cough; to kill insects. With the introduction of other efficient local anesthetics, the use of such poisons for local treatment is no longer justified. As anodyne expectorants, they are still employed to some extent, chiefly in the form of syrups from wild cherry or bitter almond oil; the former is a popular flavor for cough mixtures. For the destruction of vermin in rooms, shipholds, etc., these are filled with the vapors of hydrogen cyanide and then closed tightly for a day or two. Caution must be exercised in reopening the rooms, and several accidents have occurred by carelessness. More recently it has been found that intravenous injection of sodium cyanide produces an exceedingly efficient stimulation of the respiration in emergency, although the effect is rather brief, and there is always great danger, regardless of the fact that the fatal dose is very much larger than that required for stimulation.

The wide use of cyanides in the arts produces fairly *frequent poisoning*, and they have also been used for murderous and suicidal purposes. If the dose has been large, as is usually the case, the victim falls with a cry within a few seconds and dies very shortly after, without other notable symptoms than one or two convulsions. With smaller, but fatal, amounts, the symptoms are headache, confusion, muscular weakness, difficulty in breathing, dilated pupils, unconsciousness, violent convulsions, involuntary evacuations, and failure of the respiration. These effects, which start within a very few minutes, ensue so rapidly that death is seldom delayed more than a half hour. The cyanides quickly disappear from the body, so that, if the patient survives an hour, recovery is the usual rule. In spite of this, the mortality is exceedingly high, probably more than 90 per cent.

Because of the rapidity of action, *treatment* must be instituted promptly if life is to be saved. In case large quantities of the salts or other absorbable sources are in the stomach, chemical antidotes and evacuation may be necessary. The most useful antagonists are hydrogen peroxide, potassium permanganate, or other oxidizing agents for the poison in the stomach. For systemic counteraction, methylene blue, sodium thiosulfate, and nitrites have been employed, individually and in combination. Artificial respiration as long as the heart beats may save life, and other stimulants may be used.

THE CIRCULATION

Digitalis Group

The digitalis group of drugs exerts a powerful and significant series of effects upon the circulation, which can be used therapeutically for a number of purposes. All members of the group are qualitatively alike, although quantitative and relative differences make some of them more important than others. The most influential actions are stimulation of the vagus, with consequent slowing of the beat, increase of tone, excitability, and contractility of cardiac and vessel muscles, diuresis, and nausea. Since digitalis is the most important member, its properties and uses will first be described in detail, and the differences of the other drugs then pointed out.

1. Digitalis

Digitalis (Foxglove), U.S.P., B.P. The dried leaf of *D. purpurea* (*Scrophulariaceæ*).

Powdered Digitalis, U.S.P., B.P. Dose: 0.1 Gm., 1½ grains, U.S.P.; maximum 3 grains.

Infusion of Digitalis, N.F., B.P. Dose: 6 cc., 1½ fluidrachms, N.F.

Tincture of Digitalis, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Extract of Digitalis, N.F. Dose: 0.03 Gm., ½ grain.

Crude Digitalein, N.R. A mixture of the glucosides. Dose: 1 to 2 mg. two to three times a day.

French Digitalin (Digitaline Chloroformique, Amorphous Digitalin), N.R. Dose: 0.2 to 6 mg. daily, with caution.

German Digitalin, N.R. Dose: 2 to 4 mg.; maximum daily 20 mg.

Digalen (Cloetta), N.R. Dose: 1 to 2 cc.; maximum daily 6 cc.

Digitoxin (Crystallized Digitalin Nativelle), N.R. $C_{34}H_{54}O_{11}$. Dose: 0.5 to 1 mg. daily.

Digipoten, N.R. A mixture of the glucosides diluted with lactose. Dose: as for digitalis.

Digitan (Digipuratum), N.R. A preparation said to contain digitalin and digitoxin in the form of tannates. Dose: as for digitalis.

Digitol, N.R. A fat-free tincture. Dose: 0.3 to 1 cc.

Digifoline, N.R. Dose: 0.1 Gm. four times a day.

Applied locally to the skin, digitalis may occasionally cause smarting but usually is not irritating. On mucous membranes, however, it will produce considerable discomfort: in the eye, intense congestion and pain; in the mouth, burning pain; and in the nostrils or throat, sneezing, coughing, and inflammation. As would be expected, therefore, hypodermic injections are always painful and sometimes cause a great deal of inflammation, which may become actively septic. The irritation is very liable to set up a similar condition in the alimentary tract, when the drug is given by mouth, with the usual gastro-enteritis.

It is partially and slowly *absorbed* after oral administration, more rapidly if the dose is larger, but always quantitatively uncertain. With a single dose, several hours may elapse before any effect is noted, and the maximum action will probably be reached only after 24 to 36 hours. The rectal route gives absorption much more quickly and completely, while intramuscular and intravenous injections are nearly quantitative. The *excretion* or destruction is apparently very much slower, and it may be several days or even weeks before a single dose ceases to exert its action. With continued administration, there will always be an accumulation, regardless of the delayed absorption. For this reason the dosage is reckoned in total, without regard to the size of any single one.

The *physiological action* after absorption is exerted mainly on the nervous system and heart. The effect on the latter overshadows any other unless toxicity ensues. The most prominent result is a powerful persistent stimulation of selected medullary areas, including the vagus, the vomiting center, the heat regulation, the respiration, and the reflexes. The excitation persists until near death when toxic amounts have been administered. In addition there is a peripheral stimulation of the vagus which is usually not apparent with therapeutic doses unless certain types of heart disease exist. The vagal action is evidenced by greater dilation, longer diastolic pause, and the other effects which are usually brought about in this way. At the same time, digitalis also gives more complete systolic action, so that the filling and emptying are at a maximum. This is accomplished by direct increase of tone and contractility of the cardiac muscle. The total therapeutic effect, then, is a slower and stronger heart beat, with more output of blood per minute, a normal rhythm, and better compensation, which relieves dropsies and causes irregularities and congestion to disappear. There is very little effect upon the normal heart except slowing, but, in cases of cardiac disease, fatigue, or overwork, the results are often remarkable. If a larger dose is taken, the same action brings about a second stage of irregularities in diastole, with less output per minute, while toxic amounts give a very rapid pulse, increased irritability of the muscle, and arrhythmic heart action, finally resulting in sudden heart failure.

Digitalis also exerts some lowering of abnormal temperature and an increased coagulability of blood which are not important in therapy. There is little effect upon the *vasomotor center* with anything but very large doses, but the vessel *muscles* are acted upon directly, the result depending upon the region in question. The renal vessels are generally dilated, while those of the intestines and liver are contracted, and those of the surface are unchanged. Nevertheless, the increased output of blood from the heart should give a rise in blood pressure, and this is experienced in animal experiments. In human beings, however, the pressure is usually unaffected, probably because of more efficient vasomotor compensation, and there may even be a fall to normal in cases where this is high. The improved circulation, the greater output per minute, and dilation of the renal vessels result in a delayed but reliable diuresis, which is very effective in dropsical heart disease and fails in nephritis, as would be expected.

Composition.—In spite of the voluminous literature which has accumulated, we are still greatly ignorant as to the nature of the potent digitalis components. Many have been the claims for isolation of representative compounds and subsequent disappointments when these were found to be mixtures or inactive. The chief difficulty appears to be the character of the substances responsible for digitalis action. They are neutral glucosides, which keep perfectly well in the leaf or fairly so in strong alcohol solution but deteriorate rapidly in water and especially in the presence of acids. One can preserve activity of the leaves almost indefinitely, and even temperatures up to

120°C. do not destroy the glucosides, while infusions may lose strength as rapidly as 25 per cent in 24 hours.

Digitoxin, $C_{42}H_{66}O_{13}$, which is the most definite, exists in the leaves, not in the seeds, to the extent of about 0.3 per cent. It is crystalline, soluble in alcohol or chloroform, but not in ether or water. Ferments destroy it readily, and acids easily hydrolyze it to digitoxose (a hexose) and digitoxigenin. Digitoxin has the important actions of the crude drug but is very irritating, is very liable to give accumulative poisoning, and produces other exaggerated side effects.

Digitalin, $C_{35}H_{36}O_{14}$, is found in both the leaves and seeds. It is amorphous and soluble in alcohol but only slightly so in water, ether, or chloroform. Upon hydrolysis it forms dextrose, digitalose, and digitaligenin. It possesses only about half as much activity as digitoxin, and this is predominantly exerted in stimulation of cardiac and other smooth muscles, giving as one result a prolonged contracture, somewhat similar to that of veratrine. The name *digitalin* is often misapplied to various mixtures and extracts which are frequently inert.

Digitalein, gitalin, gitonin, digitophyllin, anhydrogitalin, digalen, gitin, digin, digitose, etc., are names given to products that are impure mixtures, inert extracts, or definite compounds with uncertain action.

Digitonin (digitosaponin) is a water-soluble compound or mixture from the seeds, which has no typical digitalis action but possesses the irritating and hemolytic properties of the saponins. A similar material from the leaves is not hemolytic.

The alcoholic solution, as represented by the tincture, gives the active ingredients of digitalis in satisfactorily stable form, but the fluidextract is very unreliable. The infusion, properly prepared, also contains a large share of the activity, but the official preparation has serious defects, and any water extract loses its strength rapidly. There was a time when the nauseant action of digitalis was attributed to various impurities in the galenicals, particularly the fat. It is now known that the nausea is an inherent property of the active ingredients and indispensable without sacrificing cardiac action. All in all, a **standardized tincture** is the best preparation for all purposes; the infusion is fairly satisfactory but deteriorates quickly and is not so readily absorbed; the leaves are too irritating. The various "pure" principles are objectionable in a number of ways; if they are active, the side actions are exaggerated. Occasionally they may be useful for certain purposes.

Digitalis is *used in therapy* in various forms of heart disease. For our purpose it is not necessary to discuss these conditions in detail, since they are largely the concern of the physician. Suffice it to say that the drug is particularly of value in cases where there are abnormalities or irregularities due to non-compensation, cardiac lesions, or insufficiency. In general, we may look upon digitalis as of particular value when a return to normal can be accomplished by better accord between working parts. The improved circulation can also be utilized to bring about diuresis in cardiac dropsies and other diseases of a similar nature, except those caused by renal disfunction. The general betterment may also aid in relieving a cough or other symptomatic condition. It might be noted that digitalis is entirely unsuccessful in reviving a poisoned heart.

There are several *methods of administration*, each of which is employed at times. Of these the most useful and satisfactory is an intensive one, in which the whole therapeutic dose is given within a short time When saturation has been reached (digitalization), often determined by beginning of toxicity (nausea), the ambulatory patient may be placed on a maintenance dosage which varies with the individual case. It probably averages from 15 to 30 minims per day, say 1 minim per hour, but can be stated as the amount that the patient can satisfactorily eliminate.

In spite of the customary belief that *poisoning* is easily attained, digitalis is not greatly important toxicologically. It is, of course, accumulative and can thus give serious effects during therapeutic treatment, but withdrawal will generally reduce the symptoms without dangerous sequel, providing the total maximum dosage has not been greatly exceeded. It might be thought that a drug which is so commonly used would often be the cause of deliberate or accidental acute poisoning, which is not the case. The Commonwealth report lists only two deaths, while other authorities give but few more, practically all of which are due to accidents in therapy. The *symptoms*, as suggested by the physiological behavior, come on after considerable delay and consist in headache, nausea, vomiting, purging, lassitude, muscular inactivity, respiratory and circulatory irregularities and failure, and death after medullary convulsions, consciousness being retained to the last. The minimum amount which would be certainly fatal cannot be stated, but it is probable that 4 to 5 grams, if allowed to be absorbed, would cause death. The treatment consists in absolute quiet and symptomatic measures.

The strength of digitalis and other materials which act in a similar way must be known with certainty; this is probably more important than with other drugs. There are several methods of making *assays* to determine this—all of them biological. The pharmacopœia has adopted the M.S.D. (minimum systolic dose) on frogs, or the amount per gram of animal which will just cause standstill of the heart in systole. Some use the M.L.D. (minimum lethal dose) for frogs or guinea pigs, while still others use the same standard on anesthetized cats, as first suggested by Hatcher. According to the reports of the International Conference on Biological Standardization, any of the methods will give satisfactory results provided it is stated which is employed.

2. Squill

Squill (Scilla), U.S.P., B.P. The cut and dried fleshy, inner scale of the bulb of the white variety of *Urginea maritima* (*Liliaceæ*).

Vinegar of Squill, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.

Fluidextract of Squill, N.F. Dose: 0.1 cc., 1½ minims, N.F.; maximum 5 minims.

Syrup of Squill, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.

Compound Syrup of Squill (Hive Syrup), N.F. Dose: 2 cc., 30 minims.

Tincture of Squill, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Oxymel of Squill, B.P.

Expectorant Mixture (Stokes Expectorant), N.F. Dose: 4 cc., 1 fluidrachm.

Scillaren, N.R. A purified mixture of the glucosides. Dose: 0.8 to 1.6 mg. three or four times a day.

Scillaren-B, N.R. A water-soluble mixture. Dose: intravenous 0.5 mg. a day maximum.

Urginin, N.R. A mixture of water-insoluble glucosides. Dose 0.5 to 3 mg. daily.

Squill is identical in action with digitalis, but the absorption is more uncertain, and a higher dosage (two or three times) is required by mouth. The emetic action appears to be very predominant; hence it was formerly employed as emetic and nauseant expectorant; the syrup is a common adjuvant for cough mixtures. Squill has been used as a diuretic, but it must be noted that the increased urine will occur only after the heart action and in full therapeutic dose. A great many authorities seem to consider the drug as more or less valueless in medicine, except where others of the digitalis group are contraindicated in heart disease. Although the chemical composition is very uncertain, scillaren and urginin, which represent more or less purified mixtures of glucosides, are used for so-called digitalis action.

Red squill is sometimes employed to poison rodents, the toxic constituent being distinct from the cardiac one.

3. Strophanthus

Strophanthus, N.F., B.P. The dried, ripe seed of *S. Kombe* or of *S. hispidus* (*Apocynaceæ*), deprived of the awns. Dose: 0.06 Gm., 1 grain, N.F.; maximum 2 grains.

Tincture of Strophanthus, N.F., B.P. Dose: 0.5 cc., 8 minims, N.F.; maximum 15 minims.

Strophanthin, U.S.P. A glucoside or mixture of glucosides obtained from *Strophanthus Kombe.* Dose: daily intravenous 0.0005 Gm., 1/120 grain, U.S.P.; maximum 1/100 grain.

Ouabain (*G. strophanthin*), N.R. A glucoside, $C_{30}H_{46}O_{12}\cdot 9H_2O$, obtained from *Acocanthera ouabaio* or from *Strophanthus gratus.* Dose: 0.5 mg. intravenously, not repeated in 24 hours.

Strophanthus is very similar to digitalis, but the action is markedly different quantitatively. All plants of the genus contain glucosides which are probably not identical, although all are given the same name, strophanthin. Each of them is hydrolyzed readily by acids to give the same or similar products; the official one yields strophanthidin, $C_{27}H_{38}O_7$, which has typical digitalis action in high degree and particularly more respiratory paralysis. Ouabain, which is by far the most active, is now appearing on the market in an especially pure state, chiefly for standardizing digitalis.

All strophanthus products have the advantages of less irritation and much less tendency to accumulation, but because of uncertain absorption from the intestines, they are unreliable by mouth. Their effects are of much shorter duration than those of digitalis. Furthermore, they are very toxic to the heart muscle and, under the conditions usually encountered, are less useful. Where digitalis cannot be used or in emergencies, strophanthin or ouabain may be administered by injection, which gives rapid result.

4. Cactus

Cactus Grandiflorus (Night Blooming Cereus), N.F. The fresh succulent stem of the wild growing *Selenicereus grandiflorus* (*Cactaceæ*). Dose: 0.5 Gm., 8 grains.

Tincture of Cactus Grandiflorus, N.F. Dose: 1 cc., 15 minims.

Although most pharmacologists agree that this drug is without definite action on the circulation, even in large doses, it has been employed for years in approximately the same conditions as digitalis, especially in dropsies and functional disorders of the heart. It is a prominent remedy in homeopathic therapy.

5. Apocynum

Apocynum (Canadian Hemp), N.F. The dried rhizome and roots of *A. cannabinum* (*Apocynaceæ*). Dose: 0.2 Gm., 3 grains.

Fluidextract of Apocynum, N.F. Dose: 0.2 cc., 3 minims.

Cymarin, N.R. A neutral, non-glucosidal substance from species of *Apocynum*. Dose: 1 to 2 mg. by mouth, 0.5 to 1 mg. hypodermically.

Cymarin is about equal to strophanthin in cardiac action. Both apocynum and its principle are poorly absorbed from the intestinal tract and in other respects have no advantage over digitalis. Cymarin is occasionally used by injection in place of strophanthin. Toxic doses cause violent emesis.

6. Convallaria

Convallaria Root (Lily-of-the-valley Root), N.F. The dried rhizome and roots of *C. majalis* (*Liliaceæ*). Dose: 0.2 Gm., 3 grains.

Fluidextract of Convallaria Root, N.F. Dose: 0.2 cc., 3 minims.

There is considerable difference of opinion as to the exact effects from this drug, but it probably has an uncertain digitalis action. It is also claimed to be non-accumulative. The chief ingredient is a glucoside, convallamarin. Convallaria and its preparations have been used for the relief of cardiac dropsy, to produce emesis or purgation, and as anthelmintics. The flowers were formerly also official.

7. Adonis

Adonis (Pheasant's Eye), N.F. The dried overground portion of *A. vernalis* (*Ranunculaceæ*). Dose: 0.125 Gm., 2 grains.

The glucoside adonidin resembles closely those of squill but is even weaker. The drug is apparently prompt in action and exhibits less cumulative tendency than digitalis. It is, however, far more uncertain and for that reason little used. Adonis has been employed with bromides in epilepsy.

8. Barium Salts

Barium Sulfate, U.S.P., B.P.

The soluble salts of barium are very toxic, producing *effects* like those of digitalis. The heartbeat is decreased but also strengthened by direct action on the muscles, and at the same time vasoconstriction brings about a remarkable rise in blood pressure. Practically all other smooth muscles are stimulated, especially those of the intestines, which produces a violent catharsis. The danger of poisoning is too great to permit any therapeutic employment of barium salts, although they are occasionally used in veterinary practice as purgatives.

Barium sulfate is tasteless and perfectly insoluble and inert to the alimentary processes. Because of these properties and because it is highly impervious to the X-ray, the salt has been replacing bismuth for diagnostic purposes.

The accidental substitution of barium sulfide for the sulfate has led to a few cases of *poisoning*. The chief symptoms are those of gastro-enteritis, with probable hemorrhages, and mild convulsions.

Other Drugs of the Digitalis Group

There are a number of drugs which have been used for the same purposes as digitalis but which are now almost obsolete. Among these are *Helleborus niger*, which has also been considered a hydragogue cathartic and emmenagogue; *Erythrophlœum guineense; Antiaris toxicaria; Acocanthera* species; *Nerium oleander; Thevetia jccotli; Cheiranthus cheiri;* and *Coronilla scorpioides.* The skin and blood of the common toad contain derivatives of cholesterol, which have been named bufanin and bufotalin, and which have a digitalis-like action. There is also an alkaloid, bufotanine, in the skin, which stimulates the vagus and all smooth muscles but also gives a high degree of respiratory and spinal paralysis. Bufagin, a substance obtained from the parotid gland of the tropical toad, *Bufa agua*, has a like action. Aconite and veratrum produce effects which are superficially similar to those from digitalis but are far from being typical, as we shall see.

CIRCULATORY STIMULANTS

The factors controlling circulation (size of blood vessels, cardiac rate and force, viscosity of blood, etc.) are so numerous that any treatment of abnormality becomes quite involved. Furthermore, drugs used for the purpose may accomplish this in a variety of ways. The most important of such substances includes the digitalis group, epinephrine, ephedrine, posterior pituitary, atropine, caffeine, strychnine, camphor, and general tonics to the metabolism. Metrazol (cardiazol) and coramine, a synthetic derivative of pyridine, have been recommended.

OXYGEN

Oxygen, U.S.P., B.P. Not less than 99 per cent of O in metallic cylinders.

Oxygen from the air is taken up by the blood to form **oxyhemoglobin,** and some in the form of solution in the plasma, the ratio of these two being about 30:1 under normal conditions. The hemoglobin is normally almost saturated with oxygen, and any increase in the pressure does not materially raise the amount absorbed in this way. The dissolved portion is altered in direct proportion to the pressure but cannot, in any event, have much influence on the total; doubling the pressure increases the whole quantity by only about 3 per cent, while the use of undiluted oxygen under ordinary conditions, which amounts to multiplying the partial pressure by 5, gives a maximum of 12 per cent increase.

The use of blood oxygen by the tissues is well defined in end-result, but the exact *mechanism* by which this is brought about is quite obscure. It is well known that this oxygen cannot of itself be efficient in the usual accomplishment but that certain enzymes of the body are essential factors and that carbon dioxide has a regulatory influence. Nevertheless, it can be assumed that the gas is equally utilizable, whether in plasmal solution or in oxyhemoglobin.

The effects of pure oxygen *administration* to normal patients, therefore, could not be expected to be large and could have no practical importance. Some slowing in the pulse and a small rise in blood pressure have been observed, but the respiration remains unchanged. As far as is known, the processes of metabolism are unaltered, and the reputed influence of oxygen on certain diseases in which there is no deficiency of this gas must be very slight. We might summarize these statements as follows: The breathing of pure oxygen for a short time has no other effect than would be obtained if the excess were replaced by inert gases such as nitrogen; excessive pressures or longer exposure, however, may give very serious results, causing pneumonia, violent convulsions, and sudden death. These are not due to pressure alone, because air or inert gases under the same conditions do not produce them.

Under certain abnormal circumstances, the breathing of pure oxygen may have a high degree of importance. These must all be referred to deficiency of saturation in the hemoglobin and to accumulation of carbon dioxide. The symptoms accompanying such conditions can be promptly relieved by oxygen administration, although the advantages cannot last any longer than the period of treatment, if the primary cause of the disease is not remedied. The *use* of the gas is indicated in cases of mechanical interference with respiration, as in threatened death by drowning, cough, or strangling; where there is diminished absorption in the lungs (lobar pneumonia); with a depressed respiratory center from poisons or anesthesia; or when the amount of oxygen in the air has been curtailed, as in mines, vaults, and anesthesia. It has also been administered in epilepsy, tuberculosis, diabetes, heart failure, and other diseases. The usual method of administration consists in supplying the gas through a mask or nasal catheter from a storage tank. Continuous injection by any route is very efficient but necessitates some technical ability and much caution.

A mixture of **helium** with oxygen is used in therapy solely because of lightness of the former as compared (one-third) with nitrogen of the air.

Ozone is an irritating poison and, while it has been proposed in some ailments, is not a substitute for air or oxygen and apparently has no place in therapy.

CIRCULATORY DEPRESSANTS

The general term is applied to anything which will reduce high blood pressure or in any other way reduces the heart action. This may be accomplished by a weakening of cardiac or vessel muscles or by action on the nervous system. The relaxation of the muscles which control the vessels is entirely reasonable and frequently resorted to, but it is doubtful whether inhibition of heart functioning is justifiable, unless this is accompanied by compensatory improvement in other respects. It would seem apparent that simple weakening of the heart is rather dangerous and unreasonable when the purpose is to bring about decreased pressure, easily accomplished in other ways. Modern medicine, therefore, has rather frowned on cardiac depressants like aconite.

1. Aconite

Aconite (Monkshood), U.S.P., B.P. The dried tuberous root of *Aconitum Napellus* (*Ranunculaceæ*). Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 2 grains.

Tincture of Aconite, U.S.P. Dose: 0.6 cc., 10 minims, U.S.P.; maximum 15 minims.

Fluidextract of Aconite, N.F. Dose: 0.06 cc., 1 minim.

Liniment of Aconite, B.P.

Liniment of Aconite and Chloroform, N.F.

Compound Dentalinament of Aconite and Iodine, N.F.

The various species of aconitum *contain alkaloids* which have similar physiological action in kind, if not in degree; indeed, many of them are claimed to be identical. The official species contains aconitine, a very unstable alkaloid, which is extremely poisonous. It is readily hydrolyzed in aqueous solution to acetic acid and benzaconine, the latter in turn to benzoic acid and aconine. Since both of the basic products are decidedly less toxic than aconitine, and since hydrolysis often takes place during isolation or during the process of manufacturing preparations, aconite and its galenicals vary enormously in strength, as would be expected. Aconitines have been encountered which differed by a ratio of 1:100, and one tincture may be a thousand times as strong as another.

Aconitine is readily *absorbed* from the alimentary tract or from other mucous membranes but not from the intact skin, unless in alcoholic or oily media. It is also readily destroyed or *excreted* from the urine and other channels and shows no tendency to accumulation or tolerance.

Applied to the skin with friction, there is some tingling and smarting, due to stimulation of the sensory nerve ends, and a later anesthesia from paralysis. Absence of reddening or inflammation is evidence that this is purely sensory. On *mucous membranes* the action is exactly analogous in greater degree. It causes a bitter taste in the mouth and a feeling of warmth, tingling, and smarting, followed by numbness and salivation. The tongue and palate feel swollen, but there are no visible signs. Similar phenomena occur in the stomach and may give rise to nausea, sneezing, coughing, etc., although these may be due partly to action on the central nervous system.

The *effects after absorption* are extremely complex, and erroneous conclusions have led to much confusion in therapy. Little effect is noted after small doses aside from some nausea and a consequent sweating, salivation, and increase in pulse. Larger amounts stimulate and then depress the nerve centers, chiefly exerted on the vagus, with resulting slow and irregular cardiac action and decrease in blood pressure. Later vagus paralysis brings about a quickened heart, and the power may become stronger from direct action of aconitine upon the muscle, although this does not take place with therapeutic amounts. At the same time, the blood pressure becomes very irregular because the vasomotor center is depressed to a greater or lesser extent. The respiratory center is markedly affected, for the breathing becomes slow and labored, with little or no evidence of primary stimulation. This depression persists even while the other portions of the medulla are still irritable, and death usually results from respiratory paralysis, occasionally from heart failure. The higher nervous centers are generally unaffected, consciousness being preserved until almost the last; any mental effect may be referred secondarily to the other actions. The dissipation of aconitine leads to tingling and numbness by peripheral action, and this may become more or less general surface anesthesia. At the same time, there are sometimes fibrillary twitchings by effect on the motor nerve ends. Secondarily, nausea increases the saliva and perspiration and produces great muscular weakness. The temperature often falls notably from the decrease in general circulation and possibly from direct action on the regulatory center. If too large amounts have been given, medullary convulsions are frequently experienced.

Aconite is *employed* as a cardiac depressant, antipyretic, and diaphoretic in certain febrile conditions of short duration and in the beginnings of other diseases but never when there is a weakened heart. The danger of respiratory or cardiac failure and the absence of benefits from the usual, ineffective doses, together with the uncertain antipyretic effects, have led to a constantly diminishing use of aconite, which was once very popular and is still a favorite homeopathic remedy. The undilute tincture, or a 10 per cent ointment or liniment, is sometimes applied locally or injected for the relief of neuralgic pain, in which case contact with mucous membranes is to be avoided. Under any circumstances, such a use must be considered very dangerous. It is claimed by some that oral administration is just as effective.

Poisonings are fairly frequent because, although it is not now a very common drug, its toxicity is extremely high. Anything more than 2 grams of aconite or 10 milligrams of aconitine would probably prove fatal. The symptoms are bitter taste, tingling and numbness in mouth and throat, salivation, nausea, vomiting, diarrhea, slow and irregular pulse and respiration, parasthesia, muscular weakness and incoordination, often convulsions, and death by circulatory or respiratory failure. The pupils are generally normal or constricted, except a later wide dilation from the asphyxia.

The *treatment* consists in the general alkaloidal antidotes, warmth, absolute quiet, the administration of diffusible stimulants like ammonia or whiskey, and possibly injection of epinephrine or strophanthin in emergencies. Artificial respiration is often a means of saving life. Atropine is a partial antidote and claimed by some as highly effective.

In consideration of the extreme toxicity, it is absolutely necessary to know the strength of any aconite preparation. Chemical *assays* for total alkaloids are useless, because there are usually present partially or wholly inactive bases. The tingling sensation in the mouth by different dilutions, or the paralysis of motor nerves by application to the eye, and other methods have been proposed, but the most logical plan is to determine total toxicity. The pharmacopœia has, therefore, chosen to direct the minimum lethal dose for guinea pigs.

2. Veratrum

Veratrum Viride (Green Hellebore, American Hellebore), U.S.P. The dried rhizome and roots of *V. viride* (*Liliaceæ*). Dose: 0.1 Gm., 1½ grains, U.S.P.; maximum 3 grains.

Tincture of Veratrum Viride, U.S.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

The activity of veratrum viride is due to a number of alkaloids, chiefly protoveratrine, with smaller amounts of jervine, rubijervine, and pseudojervine, which are practically inactive. The *physiological actions* are remarkably similar to those of aconite, being principally exerted on the medullary centers. The blood pressure is decreased, the pulse slowed, and the respiration becomes slow and labored. There is also much sweating, together with reduction of temperature, and an early tendency to emesis which renders the drug reasonably safe.

Veratrum viride is *used in medicine* as a cardiac depressant and is generally conceded to be the most reliable and safest of this group. The reduction in pressure and slowing of pulse may be of value in sthenic fevers and acute infections and, in general, like aconite.

Veratrine, a mixture of alkaloids from sabadilla seeds, is occasionally employed in decoction or ointment as antiparasitic for head lice or as local anodyne in neuralgia and is a constituent of some commercial hair washes. Although it is not so poisonous as the alkaloids of veratrum viride, caution must be exercised to prevent toxicity.

3. Sparteine

Sparteine Sulfate, N.F. $C_{15}H_{26}N_2 \cdot H_2SO_4 \cdot 5H_2O$. Dose: 0.03 Gm., ½ grain.

This alkaloid has a distinctly depressant action on the cardiac muscle. It also stimulates the vagus nerve and, to a lesser extent, the vasoconstrictor nerves. It is occasionally used to quiet an overacting heart and also in the spasms of asthma. Contrary to former belief, it is devoid of the tonic effects of digitalis.

Blood Alterations

It may be necessary to change the circulatory medium in order to alter (1) the coagulation time, (2) the pressure, (3) the volume, or (4) the composition. Since the pressure is largely dependent upon nervous or muscular control, methods of influencing it are discussed elsewhere. The total volume may be decreased by bleeding (instruments or leeches) and may be increased by transfusion or by injection of other liquids, which of course changes the composition. Absorption of drugs after any route of administration naturally alters the constituents of the blood temporarily, and any reduction or increase of cellular components in the fluid is likewise a change in composition.

The *coagulation of blood* is brought about by a complicated series of actions, all of which are not quite clear. The essential phase is transformation of fibrinogen to the insoluble fibrin by the enzyme, thrombin. The latter exists in the blood as prothrombin in combination with an unknown substance which prevents its action. It is believed that injured or bruised tissue sets free from certain cells a substance, which has been variously named but is generally called thromboplastin, and which withdraws the inhibiting substance. The prothrombin then reacts with calcium salts to produce the enzyme necessary in coagulation. In order to alter the readiness with which this coagulation takes place it is necessary only to make available more or less of these factors.

1. Calcium

Calcium Chloride, U.S.P., B.P. $CaCl_2 \cdot 2H_2O$. Dose: 1 Gm., 15 grains, U.S.P.

Ampuls of Calcium Chloride, N.F. Dose: 10 cc. (about 1 Gm.).

Calcium Lactate, U.S.P., B.P. $Ca(C_3H_5O_3)_2 \cdot 5H_2O$. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Calcium Lactate, N.F.

Syrup of Calcium Lactophosphate, N.F. Dose: 10 cc., 2½ fluidrachms.

Elixir of Calcium Lactophosphate, N.F. Dose: 8 cc., 2 fluidrachms.

Calcium Gluconate, U.S.P. $[CH_2OH \cdot (CHOH)_4 \cdot COO]_2Ca \cdot H_2O$. Dose: oral 5 Gm., 75 grains; intravenous 1 Gm., 15 grains.

Ampuls of Calcium Gluconate, N.F. Dose: 10 cc., animals 10 to 500 cc.

Precipitated Calcium Phosphate (Tribasic Calcium Phosphate), N.F., N.R., B.P. $Ca_3(PO_4)_2$. Dose: 1 Gm., 15 grains, N.F.

Afenil (Calcium Chloride Urea), N.R. $CaCl_2 \cdot 4(NH_2)_2CO$. Dose: 1 Gm. intravenously in 10 per cent solution.

The element calcium is probably a necessary constituent of all body cells and fluids, being especially abundant in the bones, the teeth, and all soft tissues. The total amount is relatively high, but very little of this is active. The circulating calcium is concentrated in the plasma, where it is remarkably constant, about 9.5 to 11 milligrams per 100 cubic centimeters. Because it is being excreted at the rate of 0.5 to 1 gram a day, mostly in the urine and sometimes in the feces, the food must contain adequate supplies. Otherwise, the skeletal and other reserves are drawn on to replace that eliminated, and ultimately a pathological condition results. The average diet furnishes much more than enough of the element, but the amount of absorption is never complete and varies considerably, owing to a variety of conditions. Whenever too little is so being absorbed, one can alter the diet or sometimes get the requisite amount by administering calcium as a salt or as an organic compound. The only certain means of insuring adequate intake is often to inject the compounds directly into the blood stream.

Lack of calcium in the body brings about important and even serious conditions. In the growing child the effect is very similar to the disease rickets, with faulty bone development, diarrhea, loss of weight, and general weakness. The adult skeleton is not affected, but other effects of faulty metabolism are just as apparent, as well as heightened actions of the central nervous system.

The *functions of calcium* must, therefore, be extensive and important. Besides being an essential for bony structure, the element is undoubtedly necessary to proper coagulation of blood fibrin. It apparently regulates the permeability of membranous tissue, and it is also probably a factor in the proper functioning of numerous organs and in the action of enzymes. Administration of calcium seems to decrease the permeability of tissue in the intestinal tract, a control of diarrhea.

When calcium salts are *injected intravenously*, it is possible to observe the effects of excessive amounts in the body, impossible to accomplish by oral administration. The chief actions are digitalis-like on the circulation, similar to that from the salts of barium, a depression of the central nervous system, contraction of the pupil, lowering of blood pressure, anuria, and respiratory paralysis.

Therapy by calcium is in a very confused and unsatisfactory condition, when one considers its great value in the body. Because the element is known to have a variety of functions, many of which have been studied carefully, clinical trials have been made in almost every known disease. The results in each case are difficult to evaluate, but it is safe to say that calcium is often administered without much chance of benefit.

Employment of the carbonate, hydroxide, oxide, and phosphate as antacids and to control diarrhea has already been noted. The chloride, lactate, and gluconate are given orally or intravenously to furnish a supply of calcium when there is proved deficiency. This may also be done in cases where excess over the normal may result in improvement, especially when used in conjunction with other agents, as in rickets and related diseases, pregnancy, lactation, and dentition. They are employed in all forms of spasmodic and nervous disorders, being of greatest value in gastric and parathyroid tetanies as temporary measures. Since calcium is an important factor in coagulation of blood, it is frequently used in hemorrhagic states, such as postpartum hemorrhage and hemophilia, in spite of there being no lack under these conditions. The explanation for most of the applications of calcium, however, rests upon decreasing the permeability of membranes, upon diuresis, and upon acidification. The most important of these are in obstructive jaundice, poisoning by lead, carbon tetrachloride, etc., inflammatory effusions and edemas, skin diseases of various kinds, serum sickness, and intestinal ailments. The value in hay fever, asthma, frostbite, boils, tuberculosis, migraine, and many other conditions is certainly not established and often may be dangerous (asthma).

Calcium has a digitalis-like action on the circulation and has been recommended as synergist for congestive heart failure and in pneumonia. Any merit under such circumstances is usually considered insignificant.

On the whole, the compounds of this element must be considered as important remedies because so often administered, even if improvement does not always follow.

2. Benzene

Benzene Medicinal (Crystallizable Benzol), N.R. Dose: 0.5 to 1 cc. four times a day.

This compound is antiseptic to a small extent and a strong poison. By inhalation, it is approximately as narcotic as chloroform, giving vertigo, delirium, convulsions, and deep sleep, often terminating in death by respiratory paralysis. Because of poor absorption, large amounts can be taken orally without more than restlessness and excitement, but frequently small doses will cause serious prostration. One of the most uniform effects after any route is the *reduction in leucocytes.*

Benzene has been *used* in influenza and other respiratory diseases, as an aromatic expectorant, as an intestinal antiseptic, as an anthelmintic, and as an external application to kill lice. The chief value today, however, is in leukemia to reduce the number of leucocytes. The clinical reports are not in agreement, and a number of fatalities have been encountered, but it is probably useful if properly administered.

3. Brain Extracts

Brain Lipoid (Impure Cephalin, Kephalin), N.R. An extract of the brain of the ox, or other mammal, according to Hirschfelder.

Solution of Brain Extract (Thromboplastin), N.R. An extract of cattle brain in saline prepared according to Hess.

Fibrinogen Local, N.R. Suspension of tissue fibrinogen and cephalin for local use.

The thromboplastin, which is such a necessary factor in blood coagulation, as has been previously mentioned, is presumed to contain cephalin most readily obtained from brain tissue. On the basis of these deductions, brain extracts were introduced as local styptics in surgery, hemorrhages, nose-bleed, etc. They are claimed to shorten the time for coagulation to about one-third. They have also been designed for hypodermic administration in order to render the blood more coagulable, but there are dangers in the procedure and very little evidence of value.

4. Nucleotide

Pentnucleotide, N.R. The sodium salts of pentose nucleotides from ribonucleic acid of yeast.

This drug gives serious reactions after intravenous injection but less marked ones intramuscularly, as usually used. The injection of 10 cubic centimeters twice daily for a few days increases the leucocyte count in cases where this is low, as in leukopenia or agranulocytosis. The value in usually fatal cases is placed very high by some.

Other Blood Alterations

The coagulability of the blood is decreased locally by antipyrine, local anesthetics, chloramine, cotarnine, solution of chlorinated soda, emetine, peptone, citrates, acetates, and mercury; systemically by iodides, hirudin, and ethylene and other anesthetics. Increased coagulability of the blood has been claimed for gelatin, pectin, ceanothin, and many other drugs. Congo red and calcium salts are frequently employed for the purpose.

Phenyl hydrazine and its derivatives reduce the erythrocytes in diseases like polycythemia, for which the hydrochloride is used in doses of 1 to 2 grains. There is great danger in the method, and most authorities condemn the practice.

Those substances used in solution to replace blood in shock or poisoning are sodium chloride, soda, gelatin, and glucose. Those employed systemically to alkalize or acidify are the compounds which have the appropriate reaction, such as acids or alkalies, and the alkaline salts of organic acids. Other drugs that are supposed to exert alterative power on the blood are those which change the content of various components, such as uric acid, glucose, leucocytes, etc.

VASODILATORS AND VASOCONSTRICTORS

Those compounds which change the size of the blood vessels perform this by action on the muscles or upon the central or peripheral nerves and will be considered under the nervous system. The chief dilators are nitrites, aconite, veratrum, and alcohol, and those used to constrict the vessels are epinephrine, ephedrine, cocaine, ergot, pituitary, and cotarnine.

THE NERVOUS SYSTEM

The intricacy of the nervous system prevents any sharp classification for the drugs affecting portions of it. This is especially true for those which are chiefly central in action, because they are never completely selective. Nevertheless, we have here attempted a division based upon either the principal physiological behavior or the chief therapeutic use. For purposes of instruction, the central nervous system is separated into the spinal cord, controlling directly the reflex movements; the medulla, in which are located regulation of the vital functions and special senses; and the brain, with its three main parts—motor, perceptive, and intellectual. Radiating from these are the network of nerves which may also be affected by drugs usually at the terminations, both motor and sensory. We shall first take up those substances used chiefly for their action upon the peripheral nerves.

PERIPHERAL MOTOR PARALYZANTS

Depression of the myoneural junctions results in either of two sets of effects: relaxation of muscles controlled by them or decrease in glandular activity regulating the secretions. We may thus have an easing of muscular spasms, including mydriasis if the ocular muscle is affected; or reduction in perspiration, saliva, milk, etc. Belladonna and some other drugs are uniformly able to accomplish both of these purposes and will be described first. Others are used for but one of these two or for only a special division. Thus, for example, lobelia is employed to relax spasms of the bronchial muscle only, its effects on others not being utilized. Some of the drugs undoubtedly act centrally in part but are placed in this class for the sake of convenience.

BELLADONNA GROUP

1. Belladonna

Belladonna Leaf, U.S.P., B.P. The dried leaves and tops of *Atropa Belladonna* (*Solanaceæ*). Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Powdered Belladonna Leaf, B.P.

Extract of Belladonna, U.S.P., B.P. Dose: 0.015 Gm., 1/4 grain, U.S.P.; maximum 1 grain.

Tincture of Belladonna, U.S.P., B.P. Dose: 0.6 cc., 10 minims, U.S.P.; maximum 30 minims.

Fluidextract of Belladonna Leaf, N.F. Dose: 0.06 cc., 1 minim, N.F.; maximum 3 minims.

Belladonna Plaster, U.S.P., B.P.

Belladonna Ointment, U.S.P.

Belladonna Root, U.S.P., B.P. The dried root of *Atropa Belladonna* (*Solanaceæ*). Dose: 0.045 Gm., 3/4 grain, U.S.P.; maximum 3 grains.

Fluidextract of Belladonna Root, U.S.P., B.P. Dose: 0.05 cc., 3/4 minim, U.S.P.; maximum 3 minims.

Belladonna Suppositories, B.P.

Belladonna Liniment, N.F., B.P.

Atropine, U.S.P., B.P. An alkaloid, $C_{17}H_{23}O_3N$, chiefly obtained from belladonna. Dose: 0.0004 Gm., 1/150 grain, U.S.P.; maximum 1/60 grain.

Atropine Sulfate, U.S.P., B.P. Dose: 0.0005 Gm., 1/120 grain, U.S.P.; maximum 1/60 grain.

Tablets of Atropine Sulfate, N.F.

Lamella of Atropine, B.P.

Homatropine Hydrobromide, U.S.P., B.P. The hydrobromide of an alkaloid, $C_{16}H_{21}O_3N$, prepared from tropine and mandelic acid. Dose: 0.0005 Gm., 1/120 grain, U.S.P.; maximum 1/30 grain.

Lamella of Homatropine, B.P.

Homatropine Hydrochloride, N.R. Used in 1 per cent solution.

Eucatropine (Euphthalmine), N.R. 1, 2, 6, 6 tetramethyl 4 mandeloxypiperidine hydrochloride, $C_5H_6N(CH_3)_4{\cdot}OOC{\cdot}CHOH{\cdot}C_6H_5{\cdot}HCl$. Dose: 2 to 3 drops of 5 to 10 per cent solution instilled into eye.

Novatropine (Homatropine Methyl Bromide), N.R.

Syntropan, N.R. The phosphate of dl-tropic acid ester of 3-diethylamino 2,2-dimethyl propanol-1 $C_6H_5{\cdot}CH(CH_2OH){\cdot}COO{\cdot}CH_2{\cdot}C(CH_3)_2{\cdot}CH_2{\cdot}N(C_2H_5)_2{\cdot}H_3PO_4$.

The solanaceous group of drugs contains **five alkaloids**—atropine, hyoscyamine, scopolamine, atropamine, and belladonnine—which are closely related chemically and physiologically. No one of the plants furnishes all of these, nor does any of them contain but a single base. The behavior of belladonna is almost entirely due to atropine, although its optically active isomer, hyoscyamine, is presumed by some to be the potent ingredient, which is changed to the former during extraction. The actions of either are quite comparable, however, so we may consider the chief principle as atropine, since this is the form extracted.

Applied locally, atropine mildly depresses the sensory nerve ends to give dulling of perception and also paralyzes the ends which control various organs and muscles. The latter effect is seldom obtained by direct application, because it is difficult to reach desired sites.

Internal administration results in a number of central and *peripheral* actions which are important. By paralysis of the myoneural junctions, or intermediary between muscle and nerve, the glands of all secretions are temporarily inactivated, including saliva, sweat, milk, gastric juice, pancreatic juice, bile, and those of the nose, throat, and bronchi. The urinary output and others not controlled by the parasympathetic system are unaffected. Through a similar nerve paralysis, practically all unstriped muscles are relaxed. This action on the circular muscle of the iris results in wide dilation of the pupil and on the ciliary muscle produces impairment of accommodation, which makes near objects blurred and distant objects more distinct. The bronchi are dilated at the same time as the secretions are stopped. Among other muscles influenced in the same way are those of the esophagus, stomach, bladder, intestines, uterus, gall bladder, and ureter.

On the *central nervous system*, atropine selectively exerts a stimulation and later depression, chiefly affecting the brain and medulla. The psychic functions are little altered by therapeutic doses, but larger amounts bring about an intoxication like that from alcohol, although the mechanism is quite different. This may result in loquacity, delirium, or even violent mania. The main cerebral effect, however, is exercised on the motor centers, which become extremely irritable—so much so in fact that they are no longer controlled, and unregulated movements are caused, similar to those in which the motor areas are depressed. The respiration is not changed greatly by the usual amounts, but larger doses make it more rapid, not entirely by stimulation of the center but also indirectly from increase in carbon dioxide production and from dilation of the bronchi. Still larger quantities paralyze the respiratory center, which is the cause of death. The circulation is influenced by a complexity of reactions which make the symptoms variable and dependent upon dosage. The vessels tend to dilate by relaxation of the muscles and to contract by vasomotor stimulation, so that the total effect is generally nil, at least under therapeutic conditions. With different amounts, however, there is an alteration in size of the vessels, most apparent in those of the skin area, which are dilated. Stimulation of the vagus center causes a slowing in heart action, but the paralysis of vagus nerve ends soon predominates, to produce a greatly quickened pulse and a corresponding rise in blood pressure, previously lowered by stimulation. Toxic amounts of atropine paralyze the centers and the cardiac muscle and thus cause a marked fall in pressure. The respiration ceases, however, before the circulation is very profoundly influenced.

These central and peripheral effects make atropine a very useful drug, as well as decidedly interesting for experiments in pharmacology. It is *used in medicine* chiefly for four purposes: (1) to relax muscles, including those of the eye; (2) to check secretions; (3) to stimulate the circulation and respiration; (4) as a local sedative.

The applications to *relaxing muscular activity* are probably its most important field. In opthalmology atropine "drops" in the eye of 1:1000 or weaker solutions are sufficient to cause mydriasis in a short time, but stronger solutions have been used to paralyze the accommodation. Both of these are valuable for ocular examinations and for the treatment of certain eye diseases. There are serious objections to the method, which are overcome by employing homatropine or other synthetics, like eucatropine. Atropine is also given in average dose or higher, or the drugs containing it may be administered by mouth, for the relief of whooping cough, encephalitic parkinsonism, and asthma. The smoking of stramonium leaves is often substituted. Preparations of belladonna are frequently used to counteract spasmodic conditions of the stomach or intestines, particularly with purgatives to lessen the griping and colic. They have also been applied locally to the uterine cervix to relieve spasm during labor or dysmenorrhea and also by mouth or hypodermically in order to relax spasmodic conditions of the ureter or bile ducts and to prevent excessive bladder incontinence in children. In general, it might be stated that hypertonic states of an unstriated muscle may be benefited by belladonna or atropine locally or after oral or hypodermic administration.

The *checking of secretions* is also an important field for atropine medication. The suppression of excessive mucus in colds and bronchitis may be accomplished with a minimum dose by mouth; it is often combined with acetylsalicylic acid in tablet form. The anhydrotic action is used to prevent the night sweats of tuberculosis, for which half the usual dose is generally sufficient. Preparations of belladonna and of the other solanaceous drugs are sometimes applied locally for this purpose in the form of ointments and plasters, but it is well known that the secretion of sweat cannot be influenced in this way. In rare cases, where antisialagogue action is required and when decrease of gastric or pancreatic secretions is desired, the oral administration of atropine is effective in bringing this about.

The *stimulating effects* are best obtained by somewhat larger doses hypodermically. Atropine is considered very highly by some as a respiratory stimulant in narcotic poisoning, especially by morphine, also in whooping cough, and as a preventive of respiratory paralysis in anesthesia. Many others are convinced that this is of doubtful efficacy, and certainly it may be very dangerous. A more logical employment is found in conditions of cardiac irregularity or where excessive vagus stimulation has slowed the heart to a dangerous point, such as in poisoning by pilocarpine or muscarine. It has also been used to determine whether a condition of slow pulse is due to vagus increase and, in the same way, to diagnose typhoid fever, in which it is ineffective in raising the cardiac beat.

Belladonna plaster or liniment has long enjoyed a reputation as *local sedative*, particularly for pains of rheumatism, neuralgia, and hemorrhoids, and atropine has sometimes been injected for the same purpose. As has already been stated, the dulling of sensory nerves is quite weak, so that cocaine and its allies are now usually preferred.

Poisoning from atropine is fairly common, but, because of its slow course, fatalities are not so frequent as might be expected. It is absorbed readily from nearly all surfaces, less so from the skin, and excreted by the urine mostly unchanged but partly as tropine or oxidation products. Since the rapidity of elimination and amount of decomposition vary with different individuals, the toxic and lethal doses are far from constant; in general children are quite tolerant. The fatal amount is probably higher than 2 grains for an adult, while recovery has taken place after large doses, by instituting prompt treatment.

The *symptoms* of poisoning, which set in promptly and are partially experienced during therapeutic administration, proceed but slowly, 10 hours to several days being required before recovery starts or death intervenes. The first effects noted are dryness in the mouth and throat, hoarseness, and difficulty in swallowing. Nausea, rise in temperature, headache, giddiness, wide dilation of the pupil, and impairment of vision follow slowly, and there is frequently a flushing of the face and neck from cutaneous dilation. The respiration may be somewhat increased, and the pulse becomes very rapid, sometimes as high as 150 to 170 per minute. The patient later becomes very restless and shows signs of excitement, which soon develops into an active delirium or even mania. Occasionally tremors and convulsions occur, but more often the giddiness passes into drowsiness and coma, and death results from asphyxia.

Treatment of the poisoning is generally efficacious because of the delayed climax, the mortality being less than 20 per cent. After administering tannin or other alkaloidal antidote, any atropine in the stomach is removed by emesis or by the gastric tube. The delirium is reduced by anesthetics or by ice to the head, and morphine has been recommended in the early stages; but after the paralysis has started, it is dangerous. The peripheral actions may be offset by administration of pilocarpine or physostigmine. In the later stages of poisoning it may be necessary to inject caffeine as a medullary stimulant and to institute artificial respiration.

2. Hyoscyamus

Hyoscyamus (Henbane), U.S.P., B.P. The dried leaf, with or without the tops, of *H. niger* (*Solanaceæ*). Dose: 0.2 Gm., 3 grains, U.S.P.; maximum 5 grains.

Extract of Hyoscyamus, U.S.P., B.P. Dose: 0.05 Gm., 5/6 grain, U.S.P.; maximum 2 grains.

Fluidextract of Hyoscyamus, N.F., B.P. Dose: 0.2 cc., 3 minims, N.F.; maximum 6 minims.

Tincture of Hyoscyamus, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.; maximum 45 minims.

Hyoscyamine is readily changed to its racemic modification, atropine, under a variety of conditions, and it is difficult to obtain pure. It has properties similar to the isomer but much stronger, so that it is infrequently used internally, except as hyoscyamus preparations for correcting the action of purgatives. For ocular installation hyoscyamine has the advantage of greater power.

3. Stramonium

Stramonium (Jimson Weed, Jamestown Weed), U.S.P., B.P. The dried leaves and flowering tops of *Datura S.* (*Solanaceæ*). Dose: 0.075 Gm., 1¼ grains, U.S.P.; maximum 3 grains.

Extract of Stramonium, U.S.P. Dose: 0.02 Gm., ⅓ grain, U.S.P.; maximum 1 grain.

Tincture of Stramonium, U.S.P., B.P. Dose: 0.75 cc., 12 minims, U.S.P.; maximum 20 minims.

Ointment of Stramonium, N.F.

Fluidextract of Stramonium, N.F. Dose: 0.075 cc., 1¼ minims.

Stramonium and datura preparations sometimes replace belladonna for local sedative effects, and stramonium leaves are generally preferred to relax bronchial spasm in asthma, where they are mixed with potassium nitrate and smoked in cigarette form. The chief value seems to be, however, in encephalitic parkinsonism, epilepsy, and mania.

ANHYDROTICS

The suppression of sweat is rarely necessary in true therapy but is often of advantage to prevent odors, chiefly of the axillæ and feet. The only reliable means to accomplish this is by local drugs, such as 'alcohol, astringents, formaldehyde or dusting powders. Aluminum salts are common in commercial preparations. The internal administration of drugs like atropine, which paralyze the sweat glands, is seldom used, because of the non-selectivity and accompanying side effects. **Tellurium** compounds, which are effective, give a disagreeable odor to the breath. They have also been suggested in leprosy and syphilis. **Camphoric acid,** although sometimes employed, does not act on the glands. Thallium salts and larch agaric have also been used for the purpose.

GENERAL MUSCULAR RELAXANTS

Several substances are presumed to relax spasmodic conditions of unstriped muscles generally. Theoretically, the depression may be used for the uterus, intestines, blood vessels, bronchi, bladder, and any other smooth muscle. Papaverine and benzyl derivatives are described as general representatives of this class, although opiates and atropine are much more important for the purpose. The asthmatic remedies, including gelsemium and lobelia, are presumed to be of value because of bronchial dilation, a specific application of this general principle. Other specialized substances are those drugs, like the nitrites, used for lowering blood pressure by vasodilation, and those, like viburnum, which are credited with uterine relaxation.

1. Papaverine

Papaverine, N.R. An alkaloid, $C_{20}H_{21}NO_4$, obtained from opium. Dose: 0.03 to 0.08 Gm., daily maximum 0.5 Gm.

Papaverine Hydrochloride, N.F. Dose: 0.06 Gm., 1 grain.

Papaverine Sulfate, N.R. Dose: as for papaverine.

Among the numerous alkaloids of opium are two groups which are distinct in constitution and physiological action. The first or the phenanthrene group is headed by morphine; the second, by papaverine which is a benzyl isoquinoline derivative. The latter is without any significant central action but peripherally lowers the tone of various smooth muscles and deadens the sensory nerve ends. It is presumed to be effective in conditions where the muscle is hypertonic and not to affect function of the normal tissue. The clinical success in intestinal and gastric spasm, biliary colic, and asthma has not been high, while there is little evidence for value in whooping cough, excessive vomiting, angina, eclampsia, etc. The local anesthetic action has been employed to relieve the pain of irritating injections and on the cornea. Papaverine is given orally or hypodermically or applied locally.

Benzyl derivatives were suggested by Macht in 1918 as the simplified representatives of the action of papaverine on smooth muscle. Experimental investigations have shown that they do relax the muscles of the uterus, intestine, vessels, bronchi, bladder, and heart. They have been recommended to relax spasm of smooth muscle in intestinal colic; uretal, biliary, and vesical spasm; dysmenorrhea; high blood pressure; angina; hiccup; whooping cough; asthma; etc. The clinical results have been conflicting, because safe dosage does not allow sufficient drug to reach the site of action. The benzoate has been recommended as a local agent in scabies.

BRONCHIAL ANTISPASMODICS

Dilation of the bronchi can be accomplished by dilator stimulation or by accelerator paralysis and can also be brought about reflexly by nauseants. Epinephrine, for example, produces relaxation by stimulation of the nerves which control bronchial dilation, while lobelia does the same thing by depressing the contractile muscle. Either method can be used in whooping cough, asthma, or other violent contractions.

1. Lobelia and Tobacco

Lobelia (Indian Tobacco), N.F., B.P. The dried leaves and tops of *L. inflata* (*Lobeliaceæ*). Dose: 0.1 Gm., 1½ grains, N.F.; maximum 10 grains.

Tincture of Lobelia, N.F. Dose: 1 cc., 15 minims, N.F.; maximum 30 minims.

Ethereal Tincture of Lobelia, B.P.

Fluidextract of Lobelia, N.F. Dose: 0.01 cc., 1½ minims, N.F.; maximum 10 minims.

The first settlers in North America found lobelia in common use among the Indians. It contains an alkaloid, lobeline, which resembles very closely in physiological action the alkaloid of tobacco, nicotine. On theoretical and practical grounds, neither substance should be used in medicine, and nicotine is not, but lobelia is very popular for a number of purposes, notwithstanding the danger in its use.

Nicotine *stimulates* the entire central nervous system from above downward and all of the autonomic ganglia, but this is soon followed by *depression.* Different species of animals react variably because of distinctions in complexity of nervous system, although the result with any one class is fairly constant, in spite of the intricate mechanism by which it is produced. The autonomic nerves are impartially stimulated and then depressed, be they inhibitory or activating, and the functioning of any organ supplied with both kinds may easily be increased or decreased, or both successively. If the organ is also under close central control, there may be another complicating factor.

The *eventual result in man*, however, is usually quite uniform. Moderate doses enhance the respiration and then greatly depress it, while large doses paralyze it completely. The heart is first markedly slowed by a combination of central and peripheral stimulation of vagus, and the blood pressure rises. With larger amounts the cardiac action is increased in rate, although becoming irregular, but the pressure remains high until the peripheral paralysis is complete. The secretions are augmented temporarily but soon cease entirely. This chiefly affects the saliva, sweat, and bronchial mucus and does not alter urine and bile. Nausea and vomiting and diarrhea are caused by muscular contraction locally, partially by action on the medullary center. Other smooth muscles react variously; the bladder is thrown into spasm, and the uterus, bronchi, and pupil are first constricted, then dilated.

Nicotine is *one of the most rapid of poisons*, being equalled, in this respect, only by prussic acid among the common substances. The mortality also is very high. The interest in its toxicity rests in the use of tobacco and preparations as sprays for plant insects and in attempts to use it as a remedy for disease. The *symptoms* from just fatal doses are salivation, nausea, and vomiting, palpitation, prostrations, and clonic convulsions. With large doses there may be merely a sudden collapse. The *treatment* consists in the administration of stimulants and in otherwise combating the symptoms.

Lobelia, like nicotine, stimulates and then paralyzes the central nervous system and the autonomic nerves. Small doses enhance the respiration somewhat, relax the bronchi, increase the flow of saliva, dilate the pupil, slow the pulse, and increase the blood pressure slightly. Larger amounts raise the latter still more and incite nausea and vomiting, with dangerous collapse. Toxic amounts act exactly like nicotine, but the emesis is earlier and stronger, removing much of the danger.

Lobelia is *used* as a nauseant expectorant and antispasmodic in croup, bronchitis, or asthma and often is smoked with other drugs. As an emetic, it was formerly employed in doses about four times larger. For this purpose it is effective but is too liable to give alarming depression and has been practically abandoned. The eclectics prescribe it in a number of convulsive conditions like epilepsy and lockjaw and in a few infectious diseases, such as diphtheria and quinsy. Many authorities consider it an unreliable drug, and certainly it is not safe. The tincture is applied locally in rhus posioning and on infectious eruptions. Alpha lobeline is sometimes employed as a respiratory stimulant.

In this connection it would be well to note the facts about smoking tobacco. For a century or more the pros and cons have been maintained recklessly and with little adherence to proved data. The antis claim that sequels to smoking include a host of ills, the more serious of which are amblyopia, changes in blood pressure, angina, arteriosclerosis, coronary occlusion, tuberculosis, cancer, gastric ulcer nervousness, sterility, liver disease, and moral degeneration. No definite statement can be made about any of these, since none is proved or disproved. No one can say with certainty that any smoker will surely contract a particular disease, although he may be more susceptible to some than the non-smoker. From a conjectural standpoint, it would seem logical to assume that continual addiction to smoking should be detrimental in some way, but it is impossible at present to go further.

Conium (poison hemlock) and its alkaloid, coniine, are similar to tobacco and nicotine.

2. Gelsemium

Gelsemium (Yellow Jasmine or Jessamine), N.F. The dried rhizome and roots of *G. sempervirens* (*Loganiaceæ*). Dose: 0.03 Gm., ½ grain, N.F.; maximum 2 grains.

Fluidextract of Gelsemium, N.F. Dose: 0.03 cc., ½ minim.

Tincture of Gelsemium, N.F. Dose: 0.25 cc., 4 minims, N.F.; maximum 20 minims.

Extract of Gelsemium, N.F. Dose: 0.01 Gm., ⅙ grain.

Gelsemium contains gelsemine, an alkaloid with a weak, strychnine-like action; **gelseminine** which is the chief principle; and several other bases. Gelseminine dilates the pupil upon local application, probably by a mechanism similar to that of atropine. Administered internally, it paralyzes the ganglia of certain motor nerves and depresses powerfully the central nervous system, chiefly the respiration. None of these effects explains the therapeutic uses.

The drug is *used* chiefly as a remedy in neuralgia, headache, and toothache and as an antispasmodic in chorea, asthmatic cough, hysteria, and uterine spasms. Occasionally a mixture of the alkaloids is used to dilate the pupil.

Even small doses sometimes cause *alarming symptoms*, and large amounts may be fatal after some delay. The symptoms are similar to those encountered in nicotine poisoning, death occurring by direct respiratory failure.

3. Grindelia

Grindelia, N.F. The dried leaves and flowering tops of *G. camporum*, of *G. cuneifolia*, or of *G. squarrosa* (*Compositæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Grindelia, N.F. Dose: 2 cc., 30 minims.

The physiological action of grindelia, due probably to an oleoresin, is feeble and subject to much argument. It probably has some depressant effect upon the motor and sensory nerve ends. Because of reported relaxation of the bronchial muscle, it has been used as an antispasmodic in asthma, whooping cough, bronchitis, and other respiratory diseases. The action as stimulant expectorant and diuretic ascribed to the volatile oil may be of assistance under these conditions. The crude drug is a constituent of many asthma powders to be used by inhaling the smoke. The fluidextract is often applied locally as a sedative in burns, rhus poisoning, inflammations, ulcers, etc.

Uterine Relaxants

1. Viburnum

Viburnum Opulus (High Bush Cranberry Bark, Cramp Bark), N.F. The dried bark of *V. Opulus* var. *americanum* (*Caprifoliaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Viburnum Opulus, N.F. Dose: 2 cc., 30 minims.

Compound Tincture of Viburnum, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Elixir of Viburnum Opulus, N.F. Dose: 4 cc., 1 fluidrachm.

Viburnum Prunifolium (Black Haw), N.F., B.P. The dried bark of the root of *V. prunifolium* (*Caprifoliaceæ*). Dose: 2 Gm., 30 grains, N.F.

Fluidextract of Viburnum Prunifolium, N.F., B.P. Dose: 2 cc., 30 minims, N.F.

Elixir of Viburnum Prunifolium, N.F. Dose: 4 cc., 1 fluidrachm.

These two drugs have been the subject of much discussion, usually lacking in scientific background until a few years ago. In spite of the fact that investigations have demonstrated that they have almost no physiological action whatever in the doses used and that very large amounts depress the central nervous system without any influence on the uterus, the two viburnums are still frequently employed as uterine stimulants and sedatives. Any diseased condition peculiar to women is presumed to be benefited, and practically every patent medicine for this purpose contains one of the two. They are generally combined with other doubtful drugs, where any virtues are probably due to alcohol.

2. Aletris

Aletris (Unicorn Root, Star Grass), N.F. The dried rhizome and roots of *A. farinosa* (Liliaceæ). Dose: 2 Gm., 30 grains.

Fluidextract of Aletris, N.F. Dose: 2 cc., 30 minims.

In small doses aletris is a simple bitter; in large amounts, cathartic and emetic; but it is mostly combined with other drugs as a treatment for female diseases. In folk medicine and homeopathy it is evidently thought to be useful in colic and rheumatism.

3. Pulsatilla

Pulsatilla (Pasque Flower), N.F. The dried herb of *P. vulgaris, P. pratensis*, or *P. patens* (*Ranunculaceæ*). Dose: 0.3 Gm., 5 grains.

Tincture of Pulsatilla, N.F. Dose: 2 cc., 30 minims.

All of the species probably contain anemonin, a lactone, or a similar compound. They are very irritating to mucous membranes, producing in the alimentary tract diarrhea and vomiting, with excessive pain. After absorption, there seems to be a powerful paralysis of the spinal cord and, perhaps also, the medulla.

Many of the erroneous statements in the literature in regard to the medicinal virtues of this drug are an outgrowth of ancient times, when it was credited with value in a host of diseases, especially of the alimentary tract, uterus, skin, eye, and nervous system. It is now sometimes prescribed by the homeopath as a sedative to the uterus and to female and male genital organs and to depress other muscles, as in asthma.

4. Caulophyllum

Caulophyllum (Blue Cohosh, Squaw Root, Papoose Root), N.F. The dried rhizome and roots of *C. thalictroides* (*Berberidaceæ*). Dose: 0.5 Gm., 8 grains.

Fluidextract of Caulophyllum, N.F. Dose: 0.5 cc., 8 minims.

The chief ingredient is a saponin which is responsible for any virtues. The drug and impure extracts are used by the eclectic and homeopathic practitioners for a number of purposes, but there is little clinical or experimental evidence available, and the claims for it are often contradictory. It is usually described as an emmenagogue, antispasmodic, and sedative for uterine conditions and as a diuretic and anthelmintic. Caulophyllum is frequently found in commercial female remedies, associated with viburnum and hydrastis.

5. Scutellaria

Scutellaria (Skullcap), N.F. The dried, overground portion of *S. lateriflora* (*Labiatæ*). Dose: 1 Gm., 15 grains.

Although practically devoid of physiological action, scutellaria has been used as a remedy for hydrophobia, neuralgia, chorea, delirium tremens, and other convulsive maladies and as a tonic sedative to the nerves in hysterical conditions. Almost the only employment today is as an ingredient of sedative mixtures, especially in uterine disorders.

6. Dioscorea

Dioscorea (Wild Yam Root), N.F. The dried rhizome of *D. villosa* (*Dioscoreaceæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Dioscorea, N.F. Dose: 4 cc., 1 fluidrachm.

The rhizome and preparations are used by the eclectic in bilious colic as a carminative; in rheumatism; and in spasmodic conditions, particularly of the uterus. It is an ingredient of viburnum galenicals.

7. Helonias

Helonias (False Unicorn), N.F. The dried rhizome and roots of *Chamælirium luteum* (*Liliaceæ*). Dose: 2 Gm., 30 grains.

The drug has a bitter and slightly astringent taste and is used chiefly as an ingredient of female remedies.

VASODILATORS

1. Nitrites

Amyl Nitrite, U.S.P., B.P. Chiefly isoamyl nitrite, $C_5H_{11}NO_2$. Dose: by inhalation 0.2 cc., 3 minims, U.S.P.; maximum 5 minims.

Spirit of Glyceryl Trinitrate (Spirit of Nitroglycerin, Spirit of Glonoin, Solution of Trinitrin), U.S.P., B.P. An alcoholic solution containing about 1 per cent of $C_3H_5(NO_2)_3$. Dose: 0.06 cc., 1 minim, U.S.P.; maximum 2 minims.

Tablets of Glyceryl Trinitrate, U.S.P., B.P.

Sodium Nitrite, U.S.P., B.P. $NaNO_2$. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Tablets of Sodium Nitrite, N.F.

Spirit of Ethyl Nitrite (Spirit of Nitrous Ether, Sweet Spirit of Nitre), U.S.P., B.P. An alcoholic solution of ethyl nitrite containing not less than 3.5 per cent and not more than 4.5 per cent of $C_2H_5NO_2$. Dose: 2 cc., 30 minims, U.S.P.

Diluted Erythrityl Tetranitrate (Tetranitrol), U.S.P., B.P. About 50 per cent of $C_4H_6(NO_3)_4$. Dose: 0.03 Gm., ½ grain, U.S.P.

Nitroglycerin and erythrol tetranitrate are not nitrites but give a similar effect, presumably being reduced in the body before action. For that reason they are here classed as nitrites.

Amyl nitrite acts selectively *on unstriated muscles,* relaxing them to a varying degree, the greatest effect being noted on the blood vessels. The exact mechanism of this action is not clear, but it is known to be exerted peripherally upon the muscles, either by paralyzing the myoneural junctions or by affecting the muscular tissue. Those of the bronchi, vessels, gall-bladder, ureter, intestines, etc., are relaxed; only the first two are utilized to any extent in medicine. The most important effect is a rapid and large fall in blood pressure, first observed in a flushing of face and neck and rapidly extending to other parts of the body, particularly the coronary veins. Indirectly, the pulse is increased by reduction in pressure, offering less resistance. The respiration also is accelerated because of the circulatory changes. There is little effect of the drug in therapeutic doses on the central nervous system. Larger amounts produce toxic results by direct paralysis of the cardiac muscle, but death is due to asphyxia and the formation of methemoglobin.

The **other nitrites** are precisely similar to the amyl derivative, with quantitative differences only, and the nitrates act in the same way after reduction. Amyl nitrite by inhalation gives its full effect in a few seconds, and this lasts but a short time, 5 to 10 minutes. The other preparations, which are given by mouth, are effective in 5 to 30 minutes and for varying periods up to 3 or 4 hours. Hypodermically they act somewhat more rapidly.

These compounds *are of service* in any condition where lowering of blood pressure is an advantage. They are also used to relieve an overworked heart, in seasickness, as antidote for cyanides, to relieve gastric pain and motility, as diagnostic aid in gastric and circulatory disorders, for the spasms of angina pectoris, and to prevent asthmatic attacks by bronchial dilation. For the last purpose, the smoking of cigarettes containing nitrates accomplishes this through the nitrite formed during burning. They have been suggested as restoratives in anesthetic accidents, in hemorrhage to reduce blood pressure, and in epilepsy, all of which suggestions seem irrational. Amyl nitrite is put up in glass "pearls," one of which is wrapped in a handkerchief, broken, and inhaled when a dose is required. The others are generally given in tablet form by mouth for sustained effects; nitroglycerin sometimes by hypodermic injection. **Sweet spirit of nitre** is a popular diaphoretic in the mild fevers of children, being also presumed to cause diuresis, and is a carminative in colic. Alcohol is probably the most active ingredient in the majority of commercial products.

Any of the nitrites can easily cause *poisoning*, but only nitroglycerin is important because of its use in the manufacture of explosives. Even in therapeutic doses, it may cause headache and dizziness, sometimes excessive sweating. Large amounts give these accentuated, together with nausea, vomiting, diarrhea, cyanosis, slow and irregular pulse, cerebral convulsions, and death from asphyxia after several hours. The treatment must be symptomatic. Strong coffee and artificial respiration are most important. Occasionally persons have idiosyncrasies, resulting in skin eruptions or visual disturbances from therapeutic doses.

2. Thiocyanates

Potassium Thiocyanate (Potassium Sulfocyanate), N.F. KCNS. Dose: 0.3 Gm., 5 grains.

Sodium Thiocyanate, N.F. Dose: 0.3 Gm., 5 grains.

Elixir of Sodium Thiocyanate, N.F. Dose: 4 cc., 1 fluidrachm.

The thiocyanates are similar to iodides in action, the chief result being a definite lowering of blood pressure by a mechanism which is not clear. There is no proof that this is of any permanent value in cases of hypertension, and this fact, together with possible toxicity, has prevented any wide application. If the dosage is adequate to reduce pressure, a large percentage of patients present symptoms of accumulative poisoning, sometimes fatal. Weakness, vertigo, coryza, dermatitis, gastric disturbance, psychoses, and convulsions are among the effects which have been noted. Renal disease and arteriosclerosis are definite contraindications.

Applications in other ways are unimportant. They have been recommended in sickle-cell anemia, bacillary dysentery, mental disorders, etc. The suggestion from theoretical reasoning, apparently erroneous, that thiocyanates should be curative in narcotic addiction is discredited.

Other Vasodilators

Choline derivatives have been studied considerably and probably have a limited usefulness in medicine. The chief application is to dilate the vessels in vascular and cardiac disorders, but they have also been recommended for abdominal paralysis, tubercular sweating, arthritis, amblyopia, and other conditions. The most important compound is acetyl beta-methyl choline (mecholin or mecholyl).

Summary of Motor-nerve Paralyzants

1. Generally to check secretions and relax muscular spasms: the belladonna group.
2. Mydriatics: homatropine, atropine, scopolamine, epinephrine, ephedrine, ergotamine, cocaine.
3. Anhydrotics: local agents, belladonna group.
4. To relax unstriated muscles: belladonna group, morphine, papaverine, benzyl derivatives, benzaldehyde.

5. To check bronchial spasm: morphine, epinephrine, belladonna group, ephedrine, chloroform, ether, cyanides, the lobelia group, nitrites, all hypnotics and sedatives.
6. To relax the uterine muscles: belladonna, morphine, the viburnum group, all sedatives.
7. Vasodilators: nitrites, alcohol, aconite, nauseants, iodides, thiocyanates, choline derivatives.

PERIPHERAL MOTOR STIMULANTS

Those drugs which are used to stimulate the peripheral motor ends are numerous and varied in their actions and exhibit differences in the effects produced. Epinephrine, for example, increases the contractility of the vascular system by sympathetic stimulation to raise blood pressure, while pilocarpine raises the tone of glandular activity, increasing secretions. As far as possible, they are grouped according to the mechanism of their chief therapeutic use. As is the case with the previous class, the drugs stimulate either muscular action or the secretions.

EPINEPHRINE GROUP

1. Epinephrine

Epinephrine (Adrenalin, Suprarenin, Suprarenalin), U.S.P., B.P. 1-methylaminoethanolcatechol, $C_9H_{13}O_3N$. Dose: hypodermic 0.0005 Gm., 1/120 grain, U.S.P.; maximum 1/50 grain.

Solution of Epinephrine Hydrochloride (Hydrochloric Solution of Adrenalin), U.S.P., B.P. Dose: hypodermic 0.5 cc., 8 minims, U.S.P.

Ampuls of Epinephrine Hydrochloride, N.F. Dose: 1 cc. (about 0.001 Gm.).

The medullary portion of the *suprarenal glands* has long been known to contain a principle which produces a powerful influence on the blood vessels. This was isolated independently by Abel and Takamine, and called adrenalin or epinephrine, in 1901. Its chemical constitution was determined a few years later, and its artificial production accomplished shortly after. While the natural substance is levorotatory, synthetic epinephrine was first racemic and much less active physiologically because the dextro form possesses little activity. The present levo synthetic is as potent as adrenalin from the gland.

Applied locally to mucous membranes, it constricts the blood vessels by a powerful stimulation of the sympathetic nerve ends

This arrests bleeding, relieves local congestion, and causes disappearance of inflammation. By mouth or hypodermically, epinephrine is rapidly destroyed and gives practically no physiological action, but *intravenously* it gives universal stimulation of all sympathetic nerves. Whether the function of a given organ or gland is increased or decreased depends entirely upon the role of the sympathetic nerves at that point. Thus, the contractions of the intestinal muscles are inhibited, while those of some blood vessels are augmented. The most important effects which are utilized in medicine are vasoconstriction, dilation of the bronchi, and cardiac stimulation. The systemic action, and to a certain extent the local as well, is very brief because of rapid destruction by the tissues.

The intravenous injection of a *therapeutic dose* in man results in an abrupt rise in blood pressure and a slowed heart, which is at the same time strengthened. These changes are due to stimulation of the vagus, the cardiac muscle, and the motor-nerve ends of the vessels. The effects last but a few minutes at most, when the organs return to normal. Larger doses cause glycosuria and give dangerous dilation of the heart, with edema of the lungs and death from respiratory failure.

Epinephrine is *used* chiefly as a *local application* for vasoconstrictor action. No other substance known has a more powerful effect. This is valuable in capillary hemorrhage at any accessible point, in inflammation, as an adjunct to retain and prolong the action of local anesthetics, in surgery to limit blood flow in operations on the eye, for the relief of hay fever and urticaria, and in many other ways. It may be applied for these purposes in strengths of 1:15,000 to 1:1000, in water, oil, ointment, or suppositories. Dilute watery solutions rapidly lose their strength and must be made directly before use.

Epinephrine is also injected for the relief of *asthma,* in 1:1000 solution, or sprayed on the larynx for the same purpose. Intravenous injections are often effective in threatened *shock* from operations or in dangerous depression of the heart during anesthesia, and it has been successfully injected directly into the heart cavities to revive persons already dead from accidents. In diseases characterized by deficiencies of suprarenal functions, epinephrine is useless.

The potency of epinephrine and the determination of its chemical structure led to the production and testing of numerous *other compounds* with similar composition. Practically all of them have an exactly analogous action upon the organism, but none of them is so active. Some natural substances belong to this class, including tyramine and ephedrine.

2. Ephedrine

Ephedrine (Anhydrous Ephedrine, N.R.), U.S.P. An alkaloid, $C_6H_5\cdot CHOH\cdot CH(CH_3)\cdot NH\cdot CH_3$, obtained from *Ephedra equisetina*, *E. sinica* and other species of *E.*

Ephedrine Hemihydrate, N.R.

Ephedrine Hydrochloride, U.S.P., B.P. Dose: 0.025 Gm., 3/8 grain, U.S.P.

Ephedrine Sulfate, U.S.P. Dose: as above.

Solution of Ephedrine Sulfate, N.F.

Tablets of Ephedrine Hydrochloride, N.F. Dose: 0.015 Gm., 1/4 grain.

Ampuls of Ephedrine Sulfate, N.F. Dose: 1 cc. (0.05 Gm.).

Syrup of Ephedrine Sulfate, N.F. Dose: 4 cc., 1 fluidrachm.

Ephedrin Spray, N.F.

Compound Ephedrine Spray, N.F.

Benzedrine, N.R. Racemic desoxy-nor-ephedrine, $C_6H_5\cdot CH_2\cdot CH(CH_3)\cdot NH_2$.

Neo-synephrine Hydrochloride, N.R. $C_6H_4(OH)\cdot CHOH\cdot CH_2\cdot NH\cdot CH_3\cdot HCl$ 1:3.

Kephrine Hydrochloride, N.R. $C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH\cdot CH_3\cdot HCl$.

Ma huang, a Chinese drug, has been employed in the orient for many years. Ephedrine, which was isolated by Nagai in 1887, has since been synthesized and examined very carefully from a pharmacological standpoint. According to the structure assigned to it, there are two asymmetric carbon atoms and consequently four possible isomers, all of which have been prepared. The levo form, however, as is the case with epinephrine which it resembles very closely, is much the most active and the only one utilized in medicine. As will be noted below, the action of these two compounds is very similar, except that that of ephedrine is more lasting. This is explained readily by the easy oxidizability of epinephrine, because of two nuclear hydroxy groups.

Locally applied, ephedrine produces mild contraction of the blood vessels, diminishing congestion and reducing inflammation and swelling. It dilates the pupil of the eye without much irritation and with little effect upon the accommodation, an effect that results also after internal administration.

The *systemic actions* consist in stimulation of the sympathetic nervous system, like that by epinephrine, and a direct stimulation of smooth and cardiac muscle which becomes depression with larger doses. These are brought about after any route of administration but most rapidly by intramuscular or intravenous injection. The chief effect is a lasting rise in blood pressure due to powerful vasoconstriction. There are also a dilation of the bronchi, marked mydriasis, and strengthening of the heart. Overdoses give symptoms of poisoning which are similar to those from epinephrine, but which are probably more dangerous because of their duration. The untoward effects, which are often only idiosyncrasies, include restlessness, insomnia, tremulousness, twitching, palpitation, skin eruptions.

Therapeutically, the salts are most definitely indicated for ophthalmological examinations and for reducing local congestion and swelling in rhinitis and hay fever. They are applied in about 4 per cent solution in the former and in 0.5 to 2 per cent lotion or spray in the latter. They are also used internally in asthma and whooping cough to dilate the bronchi and reduce inflammation but in many cases seem of little effect. Hypodermic injections have been given in heart disease, in conditions of shock and collapse, in hemorrhage, and in chronic low blood pressure. The evidence for value under these conditions is not yet great, and certainly the drug is far from being safe. The maintenance of blood pressure during spinal anesthesia is probably of definite value. Other applications are in seasickness, muscular atrophy, narcolepsy, and for the relief of pain in leprosy.

The synthetic derivatives which are described represent but a few of the hundreds which have been found to have an action like that of epinephrine or ephedrine. They are used locally in solution or ointment up to about 1 per cent. Benzedrine has a stimulating effect upon the psychic center which is possibly of value in narcolepsy, chronic fatigue, and generally in depressed states. Serious poisonings have occurred when students have used this property to keep themselves awake. Benzedrine is said to be useful in gastro-enteric spasm.

UTERINE STIMULANTS

1. Ergot

Ergot (Ergot of Rye, Secale Cornutum), U.S.P., B.P. The dried sclerotium of *Claviceps purpurea* (*Hypocreaceæ*), developed on rye plants. Dose: 2 Gm., 30 grains, U.S.P.; maximum 60 grains.

Prepared Ergot, B.P.

Fluidextract of Ergot, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.; maximum 60 minims.

Extract of Ergot, N.F. Dose: 0.5 Gm., 8 grains.

Ergot Aseptic, N.R. Dose: 1 to 2 cc. intramuscularly.

Gynergen (Ergotamine Tartrate), N.R. The normal tartrate of the alkaloid, $C_{33}H_{35}O_5N_5$, of ergot. Dose: 0.25 mg. hypodermically or intramuscularly, orally 1 mg. two to four times a day.

Ergotoxine Ethanesulfonate, B.P. (U.S.P. reference standard.) Dose: 0.5 to 1 mg. by injection.

Histamine Phosphate, U.S.P. A phosphate of beta-iminazolylethylamine, $C_5H_9N_3$.

Solution of Histamine Phosphate, U.S.P. Dose: by parenteral injection 0.3 cc., 5 minims.

The *chemical composition* of ergot, which is evidently very complex, has occasioned considerable debate, a vast number of investigations, and often erroneous conclusions. Quite a number of manufacturers have introduced extracts from time to time, which presumably represented the physiological properties and were named as if they were purified principles. With the exception of digitalis, perhaps no crude drug has produced so many names. The principal constituents are the alkaloids ergostetrine (ergonovine, ergotocine, ergometrine, ergobasine), ergotamine, and ergotoxine. In addition the bases ergotinine, ergotaminine, and pseudo-ergotinine are practically inert, while tyramine, histamine (ergamine), choline derivatives, etc., are present in small amounts but contribute to the total action.

Ergostetrine, isolated independently in four separate laboratories in 1935, seems to represent most nearly the physiological action of ergot on the uterus, giving a prompt, powerful stimulation. **Ergotoxine** and **ergotamine,** although probably less active, give strong stimulation of augmentory sympathetic nerves, with consequent rise in blood pressure and a marked contraction of the uterus. Ergotoxine also causes a blueing of the cockscomb and gangrene in poisoning, ergotamine to a less extent.

Tyramine stimulates the peripheral sympathetic nerves in the same way as does epinephrine, but the effect is less powerful and more prolonged, and the vasoconstriction by local application is very small. Furthermore, it constricts the bronchial muscle instead of dilating it and would be useless in asthma. The chief actions which might be used are the raising of blood pressure and the mild uterine contraction.

Histamine, as well as tyramine, is found in partially digested and putrefying food. It is soluble in water and hence found in aqueous extracts of ergot. Its physiological action, which is elicited only on hypodermic injection, is apparently very complex and little understood. The chief effects are lowering of blood pressure, which has not been satisfactorily explained, and a direct stimulation of many smooth muscles, particularly those of the bronchi and the uterus. Histamine may readily give rise to serious poisoning, with respiratory changes and convulsions, effects similar to the symptoms of anaphylaxis and of protein reactions which will be discussed later.

The *total effect of ergot* is somewhat variable, depending on concentration, composition, preparation used, dosage, and mode of administration. Given by mouth, it causes prompt and powerful contractions of the uterine muscle, an effect which may be lacking or negative if the dose is too small. The constriction prevents hemorrhage after parturition by closing the avenues to blood escape. When the drug (or its extracts) is injected intravenously, there is also a rise in blood pressure, but by other routes this is not appreciably affected. The alimentary tract is pronouncedly irritated, giving rise to nausea and diarrhea. There are also variable effects on the central nervous system, chiefly a stimulation and then paralysis of the medulla.

Ergot is *used* almost entirely *in medicine* as a preventive of postpartum hemorrhage, being administered in full dose after the placenta is expelled. It has also a favorable influence on the after-pains. Many obstetricians prescribe it as a routine measure at various other stages of labor, and it is often recommended for other uterine hemorrhages. The success under such conditions has induced a large employment as a general styptic, in spite of the known fact that the bleeding is often prolonged rather than limited in these cases. For reasons which are more or less obscure, ergot is often advocated and used in congestions of the most diverse kinds, such as that of the lungs in typhoid fever, pleurisy, and pneumonia; also in diabetes insipidus; in night sweats; and in certain heart diseases.

Acute ergot poisoning is almost always the result of attempted abortion. In a good many instances it will certainly accomplish the parturition by tetanic contractions of the uterus. At the same time there are natural impediments to successful expulsion in the majority of these, resulting in asphyxia of the fetus and grave danger to the mother. Furthermore, the doses required to be effective will most certainly bring about serious symptoms of poisoning, even if not death. The symptoms are dizziness, vomiting, diarrhea, difficulty in breathing, a weak and rapid pulse, muscular pains, tingling and itching, convulsions, collapse, and unconsciousness. If death does not occur, some of the evidences of chronic poisoning may set in, particularly the gangrene. The treatment is evacuation and then symptomatic.

Chronic poisoning by ergot is not important today but was formerly very common. The effects are of two types, convulsive and gangrenous, which were once thought attributable to separate poisons. The gangrene, which usually starts in the fingers or toes and finally results in sloughing off of the member affected, is of interest mainly because it is often a sequel to acute poisoning.

The complexity of composition and variation in quantities of the ingredients make a chemical assay almost impossible and, at the same time, render some sort of *standardizing* method imperative. The most satisfactory is the present pharmacopœial method by extent of blueing the cockscomb. It is a measure of the ergotoxine content and, to a lesser extent, that of histamine and cannot be absolute. It does, however, give results comparable with the more complicated bio-assays which have been proposed.

Ergotoxine ethanesulfonate is used almost solely as a reference standard for assay of ergot. Ergostetrine is at present writing merely experimental but will probably find a useful role shortly, since it is apparently representative of action by the crude drug. Tyramine was formerly used like epinephrine to which, as already noted, it is decidedly inferior.

Ergotamine, in the form of salts, is employed like ergot in obstetrics and also for hemorrhages generally. Its chief applications, however, have been in exophthalmic goiter, where it is presumed to lower glycemia and modify the cardiac symptoms; in migraine; in certain heart diseases; in glaucoma; and in the pruritus of hepatic or renal disease. In any case, caution is advisable to prevent ergotism.

Histamine is now commonly used as a diagnostic agent in enteric and gastric diseases (achylia) and sometimes also in tuberculosis and other respiratory states and in conditions in which the circulation has been disturbed. As a therapeutic agent, it is not known to be of value, although it has been employed in rheumatism of various kinds, in muscular pains, in varicose ulcers, in pruritus, etc. Histamine is a very powerful substance and, while safe orally, requires the exercise of caution in parenteral injections.

2. Hydrastis

Hydrastis (Golden Seal), N.F. The dried rhizome and roots of *H. canadensis* (*Ranunculaceæ*). Dose: 2 Gm., 30 grains, N.F.; maximum 45 grains.

Fluidextract of Hydrastis, N.F. Dose: 2 cc., 30 minims, N.F.; maximum 45 minims.

Tincture of Hydrastis, N.F. Dose: 8 cc., 2 fluidrachms.

Compound Elixir of Hydrastis (Alkaline Elixir), N.F. Dose: 4 cc., 1 fluidrachm.

Extract of Hydrastis, N.F. Dose: 0.5 Gm., 8 grains.

Hydrastine Hydrochloride, N.F. $C_{21}H_{21}O_6N \cdot HCl$. Dose: 0.01 Gm., ⅙ grain, N.F.; maximum 1 grain.

Cotarnine Chloride (Cotarnine Hydrochloride), N.F. The chloride of an alkaloid prepared from narcotine. $C_{12}H_{14}O_3NCl \cdot H_2O$. Dose: 0.06 Gm., 1 grain.

Golden seal contains **three alkaloids,** berberine, hydrastine, and canadine, the last in too small amounts to be important. The first two are very closely related to papaverine and narcotine of opium.

Pharmacological evidence would indicate that hydrastis is of little value in medicine, but it has a well-established reputation under certain conditions. It gives a strychnine-like stimulation of the spinal cord and circulatory effects, resulting in slowed heart and rise in blood pressure, both being unimportant. Hydrastine is probably responsible for the former; berberine, for the latter. The uterine muscle is constricted by the crude drug, also by hydrastine and cotarnine. The action is entirely analogous to that of ergot, but the ability to prevent postpartum hemorrhage is decidedly inferior.

All of the preparations have been used in various atonic and hemorrhagic conditions of the *uterus* to promote contraction and prevent bleeding. For this purpose, although they are decidedly inferior to ergot and pituitary, they are often ingredients of commercial mixtures. In hemorrhages other than those of the uterus they should be useless. Because of the content of berberine, which has an intensely bitter taste, hydrastis is an excellent *stomachic* and sometimes used in that way. It has also been credited with a favorable influence on diseased states of *mucous membranes*, especially of the genito-urinary tract. It is applied in the mouth, throat, and uterus for catarrhal conditions and given by mouth for any similar state of the mucous membrane in the alimentary tract.

The alkaloid **cotarnine** was at one time sold under the name of "stypticin," to be employed as a systemic and local hemostatic, but investigations show that it increases bleeding. The uterine constriction by cotarnine is apparently very weak, although it is still frequently prescribed in some disorders of menstruation.

3. Cotton Root Bark

Cotton Root Bark, N.F. The recently gathered air-dried bark of the root of one or more of the cultivated varieties of *Gossypium herbaceum*, or of other species of *G.* (*Malvaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Cotton Root Bark, N.F. Dose: 2 cc., 30 minims.

This drug owes any medicinal virtues to a high content of resin. It has long been used by the negroes in this country as an abortifacient, and scientific investigation has confirmed its stimulating action on the uterine muscles, somewhat less than that by ergot. It is employed in obstetrics during labor and also in the treatment of uterine hemorrhagic conditions.

4. Trillium

Trillium (Beth Root), N.F. The dried rhizome and roots of *T. erectum* or of other species of *T.* (*Liliaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Trillium, N.F. Dose: 2 cc., 30 minims.

Trillium has an irritating, bitter taste which causes salivation locally. The early settlers employed it as an astringent expectorant and stomachic, occasionally as a local stimulant in skin diseases. Today it is practically never used, except in mixture with other drugs as an ecbolic in labor and to control hemorrhages of the uterus.

Other Uterine Stimulants

Posterior pituitary is of great value in obstetrics, while quinine may have limited usefulness. Others which have been employed, chiefly to produce abortion, are tansy, thuja, pennyroyal, and apiol (parsley). Senecio (life-root) has been a favorite with the eclectics.

STIMULATION OF SECRETIONS

Promotion of greater activity of the secretory organs may be accomplished by a number of methods. Central or peripheral stimulation of the glandular organs will easily produce more secretion, although action on the centers usually gives too many side effects for practical pruposes. Pilocarpine and physostigmine are good examples of those drugs which act on the nerve ends. The latter, also, gives a paralysis of the spinal cord which precludes any application of its secretory effects. Increase of secretions, also, can be induced through dilation of the local blood vessels by irritants or heat or by central vasomotor action, as with salicylates, acetanilid, or aconite, while nauseants, poisons, or shock give the same result indirectly. Finally, an augmentation can be effected through a high intake of fluid by osmosis. Many drugs which are reputed to have value in increasing secretions merely permit, by their taste, the ingestion of large amounts of liquid.

Diaphoretics, which increase perspiration, are employed for a variety of objects, chief of which is to promote the removal of inflammatory products and of fluid collections or edemas. They can also be used to relieve overworked kidneys; to restore a disturbed circulation in colds, rheumatism, and diseases of the respiratory tract; to promote absorption of ointments; to improve dermal nutrition; and to reduce temperature. Commonly, also, sweating is efficient in reducing obesity. **Sialagogues,** which increase the saliva, are theoretically applicable to the same ends but are practically not useful. **Galactagogues,** increasing the milk flow, might be valuable under definite circumstances, but there seems to be no drug which is certainly a stimulant to the mammary glands.

1. Pilocarpine

Pilocarpine Nitrate, U.S.P., B.P. The nitrate of an alkaloid, $C_{11}H_{16}O_2N_2$, obtained from the dried leaflets of *Pilocarpus Jaborandi,* or of *P. microphyllus* (*Rutaceæ*). Dose: 0.005 Gm., 1/12 grain, U.S.P.; maximum 1/4 grain.

Pilocarpine Hydrochloride, N.F. Dose: as for nitrate.

Pilocarpine is, for all practical purposes, the peripheral antagonist of atropine. The *muscles* which are relaxed by the latter are contracted by the former, and the secretory glands inhibited are stimulated by pilocarpine. Practically all *secretions* except urine, bile, and milk are augmented, some of them like the saliva and sweat to a remarkable degree. One injection may give as much as 1/2 gallon of perspiration and more than a pint of saliva within the course of 2 or 3 hours. Even the secretions of ear-wax and of the suprarenals are increased. The muscles of the stomach, intestine, ureters, uterus, bronchi, and eye are all enhanced in tone. The peristaltic action of the intestine is especially heightened, giving repeated evacuation and painful straining. The eye effects, which are obtained by local application or by systemic administration, consist in myosis and strong contraction of the ciliary to produce accommodation for short vision. On the central nervous system, pilocarpine induces effects which are relatively unimportant, except in poisoning after large doses. The main results are vasomotor and respiratory paralysis. Symptoms of poisoning also include nausea, intense diarrhea, and muscular spasms. The alkaloid **muscarine,** from poisonous mushrooms, is similar in action.

Pilocarpine is the best *diaphoretic* known, being used orally or hypodermically in cases of excess fluid collection, especially when this is due to diseased kidneys. In cardiac dropsy or other heart diseases it must be avoided because of the after-depression; also, it must not be used when the lungs are diseased, since there may be serious results from the large increase in mucus. Because of these limitations, diaphoresis is generally produced in other ways. Pilocarpine is sometimes useful as a *sialagogue* after poisons which suppress the secretions or as an *expectorant* in dry cough and croup. It is often instilled into the eye as a weak *myotic* in various diseases, for which physostigmine is usually preferred. For this purpose 1 to 2 per cent solutions are used. It has attained considerable reputation in affections of the ear, especially in chronic deafness, but there is as yet no explanation of how it acts. The administration of the alkaloid as an *antidote* for atropine is often recommended, in spite of the uselessness except to counteract the minor symptoms. Other purposes to which the drug has been put are emmenagogue and ecbolic, hair tonic by local application, and in itching skin diseases.

2. Physostigmine

Physostigmine Salicylate (Eserine Salicylate), U.S.P., B.P. The salicylate of an alkaloid, $C_{15}H_{21}O_2N_3$, obtained from the dried ripe seed of *Physostigma venenosum* (*Leguminosæ*). Dose: 0.002 Gm., 1/30 grain, U.S.P.; maximum 1/10 grain.

Discs of Physostigmine, B.P.

The peripheral *action* of physostigmine is entirely analogous to that of pilocarpine except in minor details. The same secretions are increased to a lesser extent; the same unstriated muscles are stimulated, particularly those of the intestines and occulomotor. The pupil is strongly constricted, and the ciliary muscle is also affected to give near accommodation, both of these actions resulting on local application and easily counteracted by atropine. On the voluntary muscles there is a peripheral stimulation resulting in twitching, a reversal of the paralysis by curare and antagonized by the latter. In addition to these effects on the nerve ends, eserine has a powerful influence on the central nervous system, which is not entirely understood. It presents mainly a brief ascending stimulation, followed by a paralysis, the latter being so easily incited that internal administration is to be used cautiously.

Eserine is *used* chiefly by the ophthalmologist to treat the common eye disease, glaucoma, and for other ocular affections. It is applied locally as 0.1 to 1 per cent solution, to which may be added a local anesthetic to prevent irritation. It is sometimes given by mouth or hypodermically in full therapeutic dose to raise the tone of the intestinal muscle, where this is temporarily paralyzed, as is often the case after operation. The paralyzing action on the central nervous system has been tried as a remedial measure in epilepsy, tetanus, chorea, and strychnine poisoning. Eserine has also been used for certain heart complications of exophthalmic goiter. Prostigmine, a derivative, is claimed to be remedial in myasthenia gravis.

The symptoms of *poisoning* are nausea, vomiting, salivation, sweating, weakness, muscular twitching which may be very violent, palpitation and slow pulse, paralytic collapse, and death from asphyxia. The treatment is best accomplished by evacuation and by administration of atropine or strychnine or of other stimulants.

3. Eupatorium

Eupatorium (Thoroughwort, Boneset), N.F. The dried leaves and flowering tops of *E. perfoliatum* (*Compositæ*). Dose: 2 Gm., 30 grains.

Eupatorium has been quite popular in folk medicine, being described as bitter tonic, diuretic, and diaphoretic, in large doses as emetic and cathartic. The diaphoresis is undoubtedly dependent on nausea and is generally not attained in the usual amounts. A decoction has been used against tapeworm.

Other Diaphoretics

The diaphoretics are very common, since any saline or any nauseant will act in this way. Among the numerous substances described as used thus, attention might be called to alcohol, Dover's powder, ammonium and potassium salts, ginger, juniper, anise, fennel, aconite, veratrum, ipecac, euonymus, and guaiac. Verbena, the overground portions of *V. hastata*, and Asclepias, the root of *A. tuberosa*, were formerly official.

Local Anesthetics

Substances which are applied to inactivate the ends of sensory nerves are called local sedatives or anodynes and local anesthetics, depending upon the object intended. There is no hard and fast distinction between the terms, but it is usually understood that a local sedative or local anodyne is for the purpose of relieving pain, discomfort, or irritation, while local anesthetics are intended to prevent pain which may subsequently be produced, as in minor operations. The most efficient agents for either purpose are cocaine and its substances.

1. Cocaine

Cocaine, U.S.P., B.P. An alkaloid, $C_{17}H_{21}O_4N$, obtained from the leaves of *Erythroxylon Coca* and other species of *E.* (*Erythroxylaceæ*). Dose: 0.015 Gm., ¼ grain, U.S.P., maximum 1 grain.

Cocaine Hydrochloride, U.S.P., B.P. Dose: 0.015 Gm., ¼ grain, U.S.P.; maximum 1 grain.

Tablets of Cocaine Hydrochloride, N.F.

Lamella of Cocaine, B.P.

Krameria and Cocaine Lozenge, B.P.

Applied locally on the skin, cocaine has practically no action, although it will penetrate somewhat if there is a previous soaking of the part. On almost any other surface, however, cocaine produces a loss in sensation by a paralysis of the sensory ends. The taste buds of the tongue are affected only in part, and some other nerves seem as active as ever, but those having to do with pain perception are uniformly incapacitated. Stronger solutions may make the paralysis more or less permanent. Indeed, cocaine brings about its effects by general protoplasmic poisoning and, in sufficient concentration, inhibits or even destroys all nerve fibers. In addition to the local anesthesia, there is also a constriction of blood vessels, which is not due to action on the muscles and is yet unexplained. When it is applied to the eye, cocaine produces a mydriasis which is not so great as that by atropine and is evidently due partly to stimulation of the dilator mechanism. After internal administration, the pupil is dilated even more, so there must be also an action on the center. The reaction to light is not abolished.

After absorption, which may take place rapidly from local application or by mouth, but more by hypodermic injection, cocaine causes profound changes in the central nervous system. They may vary, however, because of their complexity, the amount given, and the mode of administration. The general effect is stimulation with later paralysis. The intellectual and motor centers are first affected, as shown in greater thought transference; increased ability to do work; abolishment of fatigue, drowsiness, and hunger; and a general feeling of well-being. This soon passes into depression, incoordination, narcosis, and cerebral convulsions. The respiration is accelerated for a time and then markedly depressed. The paralysis of this center is usually the cause of death. Small doses slow the pulse and give a rise and then a fall of blood pressure. Larger amounts accelerate the cardiac rate and raise the pressure, while toxic doses paralyze the whole circulation. The temperature rises on account of increased heat production. The alkaloid is rapidly destroyed in the body or excreted unchanged.

Cocaine is used mainly as a *local anesthetic and anodyne* in a wide variety of ways. For bloodless operations on the eye, ear, nose, and throat, it may be sponged on the surface, injected under the skin or membrane, or applied to the conjunctiva. The action starts in a few minutes and lasts as a rule 10 to 15 minutes, but the duration can be extended to an hour or more by adding to the cocaine solution a small amount (1:50,000) of epinephrine, which constricts the blood vessels and virtually imprisons the anesthetic. It is applied to the vagina, urethra, rectum, bladder, larynx, etc., to allay pain or irritation. The astringent effect is utilized against hay fever, catarrh, asthma, and coryza by swabbing or spraying the nasal passages. In itching skin diseases, it is a very effective anodyne. For similar reasons it is given orally to abolish nausea, to prevent seasickness or persistent vomiting, and to cure hiccough. For local application, the strength of solution varies from 0.1 to 5 per cent.

The alkaloid is also sometimes injected into the spinal column in order to get anesthesia of the lower trunk and extremities without loss of consciousness or motor efficiency. This method, which is called *regional* or *spinal anesthesia,* is exceedingly dangerous but may be useful where the general anesthetics are contraindicated.

Cocaine is frequently injected as a *respiratory* or *circulatory stimulant* or given by mouth to stimulate the psychic or motor centers. Opinions are divided as to its efficacy under such conditions, and the probabilities are that it has no advantages over other stimulants, such as caffeine or atropine.

Watery solutions of cocaine rapidly decompose, but solutions of the salts are somewhat more stable. Long boiling tends to hydrolyze the base into the component parts, benzoic acid, ecgonine, and methyl alcohol. It is still believed by some that this prevents sterilization of hypodermic solutions by boiling, but actually the amount of decomposition is not sufficient to be of material importance.

In any method of employment, there is always the danger of sudden *poisoning*, but individuals vary so in amount of absorption and in rapidity of elimination that it is impossible to state the quantity which will be toxic. Death has occurred from as little as 0.02 gram, and recovery has been experienced with very large amounts given by hypodermic injection. Serious poisoning more than frequently results during attempts to produce local anesthesia with minimum quantity. In such cases, the symptoms come on suddenly, with nausea, fainting, irregular breathing, and collapse; death may ensue in a very few minutes. Occasionally, toxicity may be the result of accidental or deliberate ingestion of large quantities by mouth, when the symptoms generally progress more slowly. The first effects are anxiety, restlessness, excitement, loquacity, and dizziness, very similar to alcoholic intoxication. The pulse and respiration are rapid, and the muscles are irritable. Later there are nausea and vomiting, sweating and high temperature, dilated pupils, delirium, convulsions, collapse, and asphyxia. If the patient survives for an hour, recovery ensues, but more or less severe, after-effects and depression nearly always occur. *Treatment* consists in evacuation and alkaloidal antidotes, but these are obviously futile when absorption has taken place by some other channel than the mouth. Reflex stimulation by ammonia or acetic acid, sedatives for the convulsions, artificial respiration, amyl nitrite, or any other symptomatic measure may be indicated.

Continual use of cocaine by man leads to an intense craving and some tolerance, just as is the case with morphine, and a similar history of moral and physical degeneration. Sunken eyes, pallor, melancholia, insomnia, hallucinations, and mania are but part of the sad picture which results. The addict, as with addicts to morphine, loses all sense of morality and, unlike the latter, has been known to commit fearful crimes in temporary fits of insanity. The curing of such a habit is claimed to be much more difficult than that from other "drugs" and is often unsuccessful.

Substitutes for Cocaine.—Because of the toxicity, especially the danger of sudden symptoms during local anesthesia, and of the liability of habit formation, there has been a great need of efficient substitutes for cocaine which would lack these disadvantages. Of the hundreds of compounds which have been prepared and tested to meet this need, several have been found very useful, but none meets every need; for some purposes cocaine is still supreme. As far as is known, none of the new compounds is capable of habit formation, and most of them are relatively non-toxic. It is interesting to note, however, that the most useful have been found to give about as many sudden accidents as cocaine. Some of them are much more irritating. A few are inclined to give permanent tissue injury. The most popular of the substitutes are: procaine, butyn, phenacaine, nupercaine, eucaine, and alypin; of the less soluble ones, butesin, benzocaine, and orthoform.

2. Procaine

Procaine Hydrochloride (Novocaine), U.S.P., B.P. p-Aminobenzoyldiethylaminoethanol hydrochloride, $NH_2C_6H_4COOC_2H_4N(C_2H_5)_2 \cdot HCl$.

Solution of Procaine Hydrochloride (Dental Anesthetic Solution), N.F.

Procaine Nitrate, N.R.

Tablets of Procaine Hydrochloride, N.F.

Ampuls of Procaine Hydrochloride, N.F. Dose: 1 cc. (0.02 Gm.).

Procaine Borate, N.R.

According to animal experiments, this compound is much less toxic than cocaine, but clinical experience has shown that it also frequently gives accidents during local application and with the same symptoms. It gives prompt anesthesia after injection, and the brief duration may be lengthened by combination with epinephrine, as with cocaine. It is not suitable for surface anesthesia, including the conjunctiva. For injection, it is employed in 0.2 to 2 per cent solution and, in other conditions, up to 20 per cent.

3. Butyn

Butyn, N.R. p-Aminobenzoyl-γ-dinormalbutylaminopropanol sulfate, $[NH_2C_6H_4COO \cdot CH_2 \cdot CH_2CH_2N(C_4H_9)_2]_2 \cdot H_2SO_4$.

Butyn was introduced as a substitute for cocaine in surface anesthesia, because it is almost as effective and more rapid and prolonged in action, can be used in smaller concentrations, and is non-irritating. It is relatively more toxic, but clinical experience seems to show that the concentrations required are even less poisonous. It has additional advantages in not drying the tissues, in giving no mydriasis, and in causing no vasoconstriction. Butyn is used in 2 per cent solution.

4. Phenacaine

Phenacaine Hydrochloride (Holocaine Hydrochloride), U.S.P. Ethenyl-p-diethoxydiphenylamidine hydrochloride, $CH_3C(NC_6H_4OC_2H_5)(NHC_6H_4OC_2H_5) \cdot HCl \cdot H_2O$.

Phenacaine is more rapid in action than cocaine and butyn and is used in the same way. It has perhaps also the advantages of being antiseptic and that its solutions do not suffer on being boiled. Its application is accompanied by temporary smarting, and it is probably somewhat more toxic than cocaine. It is used in 1 per cent solution.

5. Eucaine

Eucaine Hydrochloride (Betaeucaine Hydrochloride), U.S.P. $C_5H_7N(CH_3)_3OCOC_6H_5 \cdot HCl$.

Betaeucaine is more irritating, slightly slower, and less efficient than cocaine but is also much less toxic, and it does not cause mydriasis or constriction of the blood vessels. The chief disadvantage to its use is that there is no compatibility with epinephrine, whose action it apparently hinders.

6. Nupercaine

Nupercaine (Percaine), N.R. 2-butyloxyquinolinecarboxylic acid 4-diethylethylene diamide hydrochloride, $C_9H_5N \cdot OC_4H_9(2) \cdot CONH(CH_2)_2 \cdot N(C_2H_5)_2 \cdot HCl(4)$.

This compound is of the cocaine type but is about five times as toxic when injected, and it is much more active when applied locally. Since it causes vascular dilation, epinephrine should be added to its solutions. For local use the strength is 1:1000 to 1:2000. For spinal anesthesia the dose is 7.5 to 10 milligrams in 1:200 solution.

7. Alypin

Alypin, N.R. 2-benzoxy 2-dimethylaminomethyl 1-dimethylaminobutane hydrochloride, $CH_3CH_2C(C_6H_5COO)[CH_2N(CH_3)_2]_2{\cdot}HCl$.

Alypin is recommended for use in ophthalmology, rhinolaryngology, urology, minor surgery, and dentistry in solutions of 0.5 to 10 per cent strength, with epinephrine if necessary. The solutions may be sterilized by boiling, are not mydriatic, and do not affect the accommodation. Alypin has been claimed to be less toxic than cocaine, but at various times severe poisoning has occurred from small amounts, and it is often very irritating. It has achieved a special reputation for use in the urethra and bladder.

8. Apothesine

Apothesine, N.R. γ-Diethylaminopropyl cinnamate hydrochloride, $(C_2H_5)_2N\ CH_2CH_2CH_2OOC{\cdot}CH{:}CH{\cdot}C_6H_5{\cdot}HCl$.

Apothesine is, like procaine, efficient by injection but not suitable for surface anesthesia. Larger concentrations are required, and the action is much slower, but the anesthesia is usually just as complete if the amount is sufficient. The toxicity is probably about the same as cocaine, or twice that of procaine. It is employed for the same purposes in 0.5 to 5 per cent solutions, which can be sterilized by boiling, and in doses of 0.03 gram for the alimentary tract.

9. Stovaine

Amylocaine Hydrochloride (Stovaine), B.P. Benzoyldimethylaminoethylpropanol hydrochloride, $CH_3CH_2C(C_6H_5COO)(CH_3)CH_2N(CH_3)_2{\cdot}HCl$.

Stovaine is slightly stronger, much more irritating, and less toxic than cocaine and has no effect on the pupil. It has had an especially high reputation for the production of spinal anesthesia, usually combined with strychnine. While many reports of its action are favorable, there have been a number of accidents resulting in alarming collapse, and frequently the patient has more or less after-effects. Furthermore, there is always some local tissue injury. Stovaine is used in the same way as cocaine in 1 to 10 per cent solution.

10. Tutocain

Tutocain (Butamin), N.R. p-Aminobenzoyldimethylaminomethylbutanol hydrochloride $(CH_3)_2NCH_2CH(CH_3){\cdot}CH(CH_3){\cdot}OCOC_6H_4NH_2{\cdot}HCl$.

This compound was introduced with the idea of combining the advantages of cocaine and procaine. It is claimed to be much more efficient than the latter for injection, and, although it acts more slowly than cocaine for surface anesthesia, the effect is just as intense. The clinical experience has apparently shown it to be safe in both cases, but experiments on animals indicate a toxicity much greater than that of procaine. It is used in 0.2 to 5 per cent solutions, which can be sterilized by boiling for a short time.

11. Metycaine

Metycaine, N.R. Benzoyl-γ (2-methylpiperidino) propanol hydrochloride, $C_6H_4{\cdot}COO(CH_2)_3NC_6H_{12}{\cdot}HCl$.

The toxicity and action of this anesthetic are said to be about the same as of cocaine. It is used in 0.5 to 10 per cent solutions.

12. Diothane

Diothane Hydrochloride, N.R. Piperidinopropanediol diphenylurethane hydrochloride, $C_5H_{10}N{\cdot}CH_2{\cdot}CH(OCONH{\cdot}C_6H_5){\cdot}CH_2(OCONH{\cdot}C_6H_5){\cdot}HCl$.

The action is like cocaine but is presumed to last somewhat longer. It is about three times as toxic as procaine.

13. Larocaine

Larocaine Hydrochloride, N.R. p-Aminobenzoyl 2,2-dimethyl 3-diethylaminopropanol hydrochloride, $NH_2(C_6H_4CO)OCH_2{\cdot}C(CH_3)_2{\cdot}CH_2{\cdot}N(C_2H_5)_2{\cdot}HCl$.

Larocaine can be used for surface or infiltration anesthesia in the same way as cocaine and has some advantage in longer duration of action. It is used in 0.2 to 10 per cent solutions which can be sterilized by boiling.

14. Pontocaine

Pontocaine Hydrochloride, N.R. p-Butylaminobenzoyl dimethylaminoethanol hydrochloride, $C_4H_9NH\cdot C_6H_4\cdot COOC_2H_4N(CH_3)_2\cdot HCl$.

This is said to be effective on mucous membranes, being recommended in 0.5 per cent solution for the eye and up to 2 per cent solution for the nose and throat. It is injected in 1 per cent solution (1 to 2 cc.) for spinal anesthesia.

15. Ethyl Aminobenzoate

Ethyl Aminobenzoate (Benzocaine, Anesthesine), U.S.P., B.P. $NH_2\cdot C_6H_4\cdot COO\cdot C_2H_5$ 1:4. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 8 grains.

This substance, which was first introduced under the name of anesthesine, is almost insoluble in water and, hence, is not available for injections. It is used as a dusting powder and ointment (1 to 10 per cent) to allay pain in wounds, ulcers, and burns and to anesthetize membranes of the alimentary tract and other mucosa.

16. Butesin

Butesin, N.R. n-Butyl p-aminobenzoate, $NH_2C_2H_4COOC_4H_9$.
Butesin Picrate, N.R.

This compound is almost insoluble in water and hence belongs to the anesthesine class, over which it is presumed to have the advantage of greater efficiency. The picrate is partly soluble (1:1400) and may be used in the eye. The antiseptic properties are perhaps of advantage under certain conditions.

17. Orthoform

Orthoform (Orthoform New, Orthocaine, B.P.), N.R. Methyl m-amino p-hydroxy benzoate, $C_6H_3(NH_2)(OH)COOCH_3$ 3:4:1.

Being almost insoluble in water, this compound is used like butesin and anesthesine as a dusting powder, in ointment, or for treatment of the alimentary mucous membrane. In a number of cases it has given rise to severe local injury.

18. Benzyl Alcohol

Benzyl Alcohol (Phenmethylol), N.R. $C_6H_5CH_2OH$.

In saturated solution, benzyl alcohol is non-irritating, nontoxic, fairly antiseptic, and markedly anesthetic for brief periods.

It is used by injection or for surface anesthesia, as a local application in itching skin diseases, and on wounds and burns.

Other Local Anesthetics

Substances which have been on the market and which are sometimes used are: **saligenin,** or salicyl alcohol, $C_6H_4(OH)CH_2OH$, which is analogous to benzyl alcohol; **rose oil,** or benzyl carbinol, $C_6H_5CH_2CH_2OH$, and phenyl methyl carbinol, $C_6H_5CH(CH_3)OH$, which are very similar; **propaesine,** or propyl aminobenzoate, and **cycloform,** or isobutyl aminobenzoate, which are like anesthesine; **tropacocaine,** or benzoyl pseudotropine, which occurs with cocaine in coca leaves but usually is made synthetically; **allocaine-S,** similar to procaine but very irritating; **yohimbine,** from yohimba and aspidosperma.

A few drugs used for other purposes are often applied locally to relieve pain and sometimes for performing operations. Quinine urea, papaverine, aconitine, veratrine, cyanides, phenol, all astringents and counter-irritants, magnesium sulphate, chlorobutanol, chloroform, ether, alcohol, clove oil, belladonna, and ethyl chloride might be placed in this class. Hundreds of other substances have at one time or another been described as local sedatives.

ANESTHETICS

General anesthesia is useful for obliterating the perception to pain and abolishing reflexes and voluntary movement, chiefly to permit surgical operation. The discovery of means to accomplish this, which has been made since 1840, was a very important development in modern surgery.

The *ideal anesthetic* would paralyze temporarily the cerebral motor and perception centers and the spinal reflexes, without affecting the control of vital functions. It would be capable of easy administration and rapid recovery and would involve no after-effects. Such a substance is as yet unknown, because the selective action on body organs is never so sharply defined. The substances which approach nearest to this are ether, nitrous oxide, ethylene, and chloroform. The last has innumerable advantages but, unfortunately, possesses too much effect on the medullary center to be entirely safe. Since it is beyond the scope of this book to discuss fully the voluminous details of anesthesia, we can but outline the chief facts. Ether and chloroform are best considered together for convenience.

1. Chloroform

Chloroform, U.S.P., B.P. $CHCl_3$. Dose: 0.3 cc., 5 minims, U.S.P.; maximum 10 minims.

Chloroform Water, U.S.P., B.P. Dose: 15 cc., 4 fluidrachms, U.S.P.

Chloroform Liniment, U.S.P.

Spirit of Chloroform (Spirit of Chloric Ether), U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.; maximum 40 minims.

2. Ether

Ether, U.S.P., B.P. $(C_2H_5)_2O$. Dose: 1 cc., 15 minims, U.S.P.; maximum 60 minims.

Spirit of Ether (Hoffmann's Drops), N.F., B.P. Dose: 4 cc., 1 fluidrachm, N.F.

Compound Spirit of Ether (Hoffmann's Anodyne), N.F. Dose: 4 cc., 1 fluidrachm.

Ethereal Oil, N.F.

Ethyl Oxide (Solvent Ether), U.S.P.

The *induction of anesthesia* by chloroform or ether takes place in three fairly well-defined stages, and overdoses give a fourth. The usual method of initiating the operation is by preliminary injection of morphine or other narcotic or by inhalation of another anesthetic, which does not act so profoundly.

The first or *analgesic stage* presents a feeling of warmth in the face and spreading over the whole body, roaring in the ears, and a sense of asphyxia. The sensibilities are somewhat dulled, the pupils enlarged, and the pulse rapid.

The *excitement stage* is sometimes mild but often quite violent. The patient struggles to push away the operator, shouts, tries to get up, or expends his energies in abuse. There seems an endless variety to the outward manifestations; retching and vomiting often occur. The reflexes are at first exaggerated but later depressed, and at this point stimulation evokes response, but there is little pain. The respiration may have become irregular or may be suspended intermittently.

In the state of *complete anesthesia*, the face takes on a death-like appearance, the reflexes disappear, the pulse may be slower and somewhat weak, and the respiration becomes regular and sometimes noisy. The temperature falls slowly, as much as four or five degrees if the anesthesia is prolonged, and the pulse and respiration become weaker. Nevertheless, it may be kept up for hours if the drug is properly administered.

When the anesthetic is withdrawn, the *patient recovers* more or less rapidly, according to the duration of narcosis, going through the same stages in reverse order. As soon as consciousness has returned, there is usually a natural sleep which lasts several hours, sometimes nausea and vomiting, but seldom any other untoward actions.

If *overdoses* of these drugs are administered, the respiration and pulse become progressively weaker, and the body temperature falls appreciably. The breathing ceases while the heart is still beating; at this point, artificial respiration is often sufficient to revive after ether, because the heart has been subject to less injury. The inhalation of even very dilute chloroform vapor apparently leads to profound cardiac change. Frequently with chloroform, less so with ether, there are anesthetic accidents which cannot be attributed to overdosage, but which are due to reflex disturbances of the cardiac mechanism.

The *choice of anesthetic* is influenced by a number of factors. The danger from chloroform can be largely overcome by careful administration, yet its existence must always be considered. Furthermore, it often gives fatty changes in various organs, which promote fatal toxemia or diabetic coma after several days. With ether also there are such post-anesthetic effects in the liability to pulmonary edema or pneumonia. Under ordinary circumstances, ether is the agent of choice, because it is much less dangerous, but chloroform has numerous advantages which often outweigh the toxicity and so lead to a continuance of its use. It is not inflammable; is more convenient to use; more rapid and profound in action; less disagreeable to take; causes less suffocation, nausea, and excitement; and gives more muscular relaxation. Very often, too, there are contraindications to the use of ether, such as acute respiratory, hepatic, or renal disease.

Ether is frequently *used* as reflex circulatory stimulant in fainting or heart failure and as carminative and antispasmodic. The spirit is added to expectorant mixtures. Ether evaporates readily and, when sprayed on the skin, produces sufficient cooling to numb the sensory nerves and permit minor surgery. It is also a common detergent and antiseptic in surgery. It is often administered by rectum (in oil) for labor (Gwathmey), in whooping cough, and in other spasmodic conditions, such as tetanus.

Chloroform is much more antiseptic than ether and is often added to drugs as a preservative. It is a very efficient vermicide, especially for tapeworms and hookworms, but toxicity to the host prevents any extended use. On the skin and mucous membranes it causes irritation and rubefaction, which are utilized by means of the liniment as counter-irritant; also by the spirit as carminative and sedative in colic, vomiting, seasickness, cough, etc. Chloroform is often added to cough mixtures as a flavor and anodyne expectorant. **Bromoform** was formerly employed in a similar way but possesses no advantage.

Poisonings from ether or chloroform are most frequently a sequel from anesthesia but may also be brought about by deliberate swallowing of large quantities or by accidental ingestion. The symptoms in such cases are nausea, vomiting, and diarrhea, followed by the usual narcosis and asphyxia. The treatment indicated would consist of respiratory and circulatory stimulation, with artificial respiration if necessary. Apparent recovery may be followed by pneumonia or acidosis after days.

3. Nitrous Oxide

Nitrogen Monoxide (Nitrous Oxide, Laughing Gas), U.S.P., B.P. N_2O.

This gas is the oldest and *safest* of the anesthetics. Whereas the fatalities with chloroform number about 1 in 3000, and those with ether 1 in 10,000, the mortality from the use of nitrous oxide is less than 1 death in 5,000,000.

When the pure gas is inhaled through a mask, there is a rapid succession of *symptoms;* sweet taste, excitement, staggering gait, drowsiness, insensibility to pain, loss of consciousness, and cyanosis. If the administration is continued, the respiration and pulse are progressively depressed, and death finally occurs by asphyxia. If the mask is removed at the cyanotic stage, the anesthesia lasts about ½ minute, after which the patient recovers within a short time and with no after-effects. Any attempt to prolong the narcosis is dangerous, because the absence of oxygen induces asphyxia.

If *oxygen is mixed with the gas* up to about 15 per cent, the asphyxia is prevented, and the full narcotic effect can be prolonged indefinitely. In such case the induction is naturally slower, and the result less profound, but the same symptoms are experienced. Under either method, however, the reflexes are never entirely abolished, nor is the anesthesia ever so deep as with ether. The patient recovers within a minute or two and, aside from nausea, experiences no ill effects. Cases of addiction to its use are known.

Nitrous oxide is very useful for *short operations*, for the induction of ether anesthesia or for reducing the sensibilities during labor. It is administered through a special face mask from steel cylinders, into which it has been liquefied under pressure.

4. Ethylene

Ethylene U.S.P., B.P. $CH_2 = CH_2$.

Ethylene was suggested but a few years ago for use as a general anesthetic and has rapidly assumed major importance for this purpose. It apparently stands between nitrous oxide and ether, by some being considered equal to the latter in most cases and certainly deficient in the respiratory irritation and other untoward effects. The principal disadvantages are decrease in the coagulability of the blood and inflammability, although it is probably less dangerous in this respect than ether. The sequence of symptoms and absence of after-effects are similar to those from nitrous oxide.

The gas is administered by mixture with 10 per cent of oxygen, the amount of which can be raised after a prolonged period. If premedication has been used, the amount of oxygen can be still higher. It is being increasingly used for all kinds of short and long operations in place of ether. The gas comes on the market in steel cylinders.

Propylene, cyclopropane, and **acetylene** have similar properties and have been proposed as anesthetics.

5. Ethyl Chloride

Ethyl Chloride (Kelene), U.S.P., B.P., N.R. C_2H_5Cl.

Ethyl chloride is very similar to chloroform but produces prompt anesthesia which may be useful for short operations;

recovery is particularly rapid because of its volatility. The chief advantage being the speed with which induction takes place, and the consequent absence of excitement and struggling, it is frequently used in sequence with the safer ether. **Ethyl iodide** and **bromide** have been used in the same way.

Ethyl chloride is also widely used in the form of a spray for the production of *local anesthesia* in minor surgery. For this the liquid is put up in glass tubes provided with a cock for releasing it. The pain experienced afterwards limits the application to the removal of splinters, lancing of boils, etc.

6. Methyl Chloride

Methyl Chloride, N.R. CH_3Cl.

Although this substance has been used as a general anesthetic, it fails to produce complete relaxation, so it is combined with other compounds. By its evaporation there can be attained temperatures as low as −50°C., which can be employed for producing local anesthesia. It is, however, very liable to make a blister and must be applied with caution. Sometimes it is mixed with ethyl chloride in order to prevent blistering. The common application of methyl chloride in electric refrigerators has led to several cases of poisoning.

Other Anesthetics

Many materials have been tried as anesthetics with little success except with those already described. We have already seen how cocaine and its allies are utilized to produce regional anesthesia, which is limited in usefulness. Mixtures of morphine and scopolamine were once considered valuable for this purpose under the title of "twilight sleep," and mixtures of morphine and magnesium sulphate have been suggested. Chlorobutanol is often used for animals.

Tribrom-ethyl alcohol (avertin) has been employed as general and induction anesthetic for a number of years. In spite of the high value assigned to it by some, the inability to control dosage and danger of toxicity are decided disadvantages. Contraindications to its use are numerous. It is administered in amylene hydrate by rectum in dose of not over 0.1 gram per kilogram of weight.

Divinyl ether or oxide (vinethane) has recently shown excellent promise as an inhalation anesthetic.

ANALGESICS

The analgesics are agents which mitigate or abolish pain perception. They are also known as anodynes or sedatives. For convenience these terms are generally applied only to those substances which accomplish the object after absorption, and the materials which act at the point of application are called local sedatives or local anodynes. The analgesics are usually narcotics affecting the perception centers of the brain, such as morphine, but some of them, like acetanilid, diminish pain by a different mechanism which is unknown. The most useful agents of this class are morphine and its allies, the coal-tar antipyretics, and the general anesthetics.

1. Opium

Opium, U.S.P., B.P. The air-dried, milky exudation obtained by incising the unripe capsules of *Papaver somniferum* or its variety *album* (*Papaveraceæ*). Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 3 grains.

Powdered Opium, U.S.P., B.P. Dose: as for opium.

Granulated Opium, U.S.P. Dose: as for opium.

Tincture of Opium (Laudanum), U.S.P., B.P. Dose: 0.6 cc., 10 minims, maximum 30 minims.

Camphorated Tincture of Opium (Paregoric, Compound Tincture of Camphor), U.S.P., B.P. Dose: 4 cc., 1 fluidrachm, U.S.P.

Tincture of Ipecac and Opium (Tincture of Dover's Powder), N.F. Dose: 0.5 cc., 8 minims.

Extract of Opium, N.F., B.P. Dose: 0.03 Gm., ½ grain, N.F.; maximum 1 grain.

Powder of Ipecac and Opium (Dover's Powder, Compound Powder of Ipecac), U.S.P., B.P. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 20 grains.

Aromatic Powder of Chalk and Opium, B.P.

Syrup of Ipecac and Opium (Syrup of Dover's Powder), N.F. Dose: 4 cc., 1 fluidrachm.

Expectorant Mixture (Stokes Expectorant), N.F. Dose: 4 cc., 1 fluidrachm.

Lotion of Lead and Opium (Lead and Opium Wash), N.F.

Compound Mixture of Opium and Licorice, U.S.P. Dose: 4 cc., 1 fluidrachm.

Morphine Sulfate, U.S.P. The sulfate of an alkaloid, $C_{17}H_{19}O_3N$, from opium. Dose: 0.008 Gm., ⅛ grain, U.S.P.; maximum ½ grain.

Tablets of Morphine Sulfate, N.F.

Tablets of Morphine and Atropine Sulfates, N.F.

Morphine Hydrochloride, N.F., B.P. Dose: 0.008 Gm., ⅛ grain, N.F.; maximum ½ grain.

Solution of Morphine Hydrochloride, B.P.

Morphine Tartrate, B.P.

Morphine and Ipecac Lozenge, B.P.

Morphine Suppositories, B.P.

Ethylmorphine Hydrochloride (Dionine), U.S.P. The hydrochloride of an alkaloid, $C_{17}H_{18}O_2N\cdot OC_2H_5$, prepared from morphine by ethylation. Dose: 0.015 Gm., ¼ grain, U.S.P.; maximum ¾ grain.

Codeine (Methylmorphine), U.S.P., B.P. An alkaloid, $C_{17}H_{18}O_2N\cdot OCH_3\cdot H_2O$, obtained from opium or prepared from morphine by methylation. Dose: 0.3 Gm., ½ grain, U.S.P.; maximum 1 grain.

Codeine Phosphate, U.S.P., B.P. Dose: as for codeine.

Tablets of Codeine Phosphate, N.F.

Codeine Sulfate, U.S.P. Dose: as for codeine.

Tablets of Codeine Sulfate, N.F.

Diamorphine Hydrochloride (Heroine Hydrochloride, Diacetylmorphine Hydrochloride), B.P.

Dilaudid Hydrochloride, N.R. Dihydromorphinone hydrochloride. $C_{17}H_{19}O_3N\cdot HCl$. Dose: 0.002 Gm., 1/32 grain; maximum 1/20 grain.

The group of opium alkaloids undoubtedly represents the most important class of all drugs. Altogether, the opium of commerce contains more than 25 bases, of which morphine is the largest in amount and most useful, but it also contains such drugs as codeine and papaverine. They are combined in the crude drug as salts of meconic and lactic acids. Besides these, however, a number of artificial alkaloids have been produced, mostly derivatives of morphine. Dionine and dilaudid are often used. The great majority of these opiates, including morphine, are derivatives of phenanthrene and have similar physiological action, which must also naturally be the general effect when opium itself is employed. For this reason, the behavior of morphine will best be described first.

Morphine has no *local action* except a mild irritation, which may be sufficient to cause rubefaction and to dilate the cutaneous vessels; the same effect may occur after oral or hypodermic administration. Contrary to a common impression, there is no peripheral effect in muscles or nerves after local application, and the older formulas for anodyne lotions might well eliminate the opium or morphine. In the gastro-intestinal tract, however, the drug causes important actions, regardless of the route of administration. Nausea and vomiting are often induced by central action, and this may become very serious in susceptible individuals. The intestinal peristalsis is reduced, and constipation follows, an effect which is entirely peripheral and probably very complex.

The *action after absorption* is chiefly a descending depression of the central nervous system, preceded by a brief stimulation in parts and beginning with the cerebrum. The latter is depressed with the smallest doses, first observed in a dulling of sensibility to pain and discomfort, a disturbance of the intellect to some external stimuli, drowsiness, and sleep, from which there is ready awakening. With larger doses, this becomes a stupor and eventually a dangerous coma. The respiration is calmed, and the bronchi relaxed by small amounts, while larger doses constrict the latter and markedly depress the respiratory center. The cough reflex also disappears, probably by action at some other point. The circulation is undoubtedly affected as well, but, aside from a preliminary slowing and later weakening, this is relatively unimportant. The cutaneous vessels are dilated, producing diaphoresis. There is no action on the spinal centers, except with very large quantities, which may give typical strychnine-like convulsions. As a rule in man death occurs before these are encountered. The pupils are constricted to a maximum by central action, but often there is an asphyxial dilation just before death, which results from respiratory paralysis. Continued administration of morphine leads to a notable tolerance and the habit which is so familiar.

The *other narcotic bases* of opium behave in a similar way, differing only in degree. Codeine is less narcotic, less constipating, and less apt to give tolerance than morphine and does not easily induce habit. Dionine stands midway between these two and is less useful than either. Applied to the conjunctiva, it causes a local vasodilation, which is of limited service to secure absorption of inflammatory products and, presumably, to give relief from pain.

Morphine is very useful for a large number of purposes. It is unrivalled as an analgesic and hypnotic, regardless of continual attempts to produce artificially a substance that would be as efficient without the drawbacks, and regardless of the danger of habit formation. It is true that other hypnotics are today more often used, but morphine is almost always the last resort. Indeed, its employment under any circumstances should be selected only when other agents are ineffective. In convulsive diseases such as tetanus and epilepsy, chloral is generally more adequate and preferable. As a calmative to the respiration and cough reflex in asthma and dyspnea, morphine has remarkable efficacy but is usually replaced by codeine, which is often added to expectorant mixtures. In the form of Dover's powder, or other mixture with ipecac, it is used as a diaphoretic. With very little action in this way, it nevertheless is adjuvant in dilating the cutaneous vessels and in preventing nausea from the ipecac. In diarrhea and various intestinal disorders, morphine is generally very efficient to check peristalsis and to relieve discomfort or pain, but preparations of opium may be preferred because of the adjuvant papaverine group and because of slower absorption. It is also used in hemorrhage at points inaccessible to local drugs; it is of aid here by quieting the movements to allow formation of a clot. In diabetes it has been employed in fairly large doses and presumably with benefits in some cases, where it probably acts by lessening intestinal absorption. One of the most important fields is as synergist to anesthetics, both general and local. In itself it is incapable of producing complete relaxation and insensibility, without doses sufficient to give poisoning, but it reduces the amount of anesthetic required and, if given beforehand, allays apprehension and reduces excitement.

Codeine, being less narcotic and less constipating and not liable to form a habit, is especially useful in cough and as sedative for long-continued administration. It is recommended also in place of opium for diabetes and in alimentary disorders.

Ethylmorphine can replace morphine or codeine for sedative or analgesic action, but it is not often considered of any advantage. It has a special field in the treatment of eye diseases, as mentioned above; a collyrium of 5 to 10 per cent, increased to 20 per cent if necessary, may be applied directly to the conjunctiva.

Diacetylmorphine has less narcotic and more respiratory action than morphine and somewhat less effect on the intestines. It was originally introduced with the idea that there would be an advantage in cough, but investigation has shown that this is not the case. Many authorities, in fact, consider codeine much superior to heroine for all purposes. The latter is habit forming and much more toxic than any of the other derivatives, giving dangerous depression of the respiration, so that its manufacture or importation has been prohibited in this country. While present stocks remain, it will be marketed, but sooner or later we may expect a disappearance of this drug.

Dilaudid has about the same effects as morphine but in much smaller dose. At the same time, it is proportionally more toxic. It is claimed to have the advantage of less side effects, such as nausea, vomiting, and constipation.

Pantopon (pantopium), a mixture of the alkaloids of opium in their natural proportion, is used in the same conditions as the crude drug. It has the advantage of being more rapid but does contain 50 per cent of morphine.

Acute poisoning by the opium derivatives is very important because of frequent occurrence. According to the Commonwealth Report, they occupy third place, being exceeded only by alcohol and mercury. With morphine, 0.5 gram or less is apt to be fatal, and 0.1 gram may be dangerous under certain conditions. The dose of opium is approximately ten times this. People differ considerably in their reaction. Infants are very susceptible. The symptoms, which begin very shortly after ingestion, are fairly uniform. The chief ones are a sense of well-being, dizziness, confused intelligence, somnolence, slowed pulse and respiration, possible nausea and vomiting, sleep, myosis which later becomes extreme, stupor from which the patient can be partially roused, loss of reflexes, irregular pulse and respiration, pale skin, cold sweat, convulsions (especially in children), cyanosis, asphyxia, and death by respiratory paralysis 2 to 10 hours after administration.

The *treatment,* to be effective, must be prolonged and constant. The first indication is for washing out the stomach with a tube, regardless of the mode of administration, because morphine is excreted chiefly by the alimentary tract. Emetics may be employed in the early stages but may be useless if stupor has already started. Potassium permanganate solution (0.5 gram per liter) is recommended as an antidote and for washing but is not eminently successful. Since the danger is from threatened paralysis of the respiration, it is essential to guard against this by stimulants, such as caffeine, and by artificial respiration if necessary. During the first stages of narcosis, anything which keeps the patient awake will be of material assistance, because action tends to maintain operation of the lungs. Atropine is generally recommended but should never be given in doses larger than 1.5 milligrams. If the patient can be kept alive for more than 12 hours, the chances for recovery are very good.

The problem of chronic poisoning or *morphine habit* is certainly of very great importance to society but not so much so to the pharmacist. It may be started by medical treatment or accidentally but is often the result of persuasion by an addict. Among the Orientals the drug is smoked almost entirely. In this country and in Europe it is taken by mouth or hypodermically. The quantity required is at first very small, but, as tolerance is induced, the dose becomes larger and the administration more frequent, until enormous amounts are used daily. If the needed drug is unavailable, the victim is assailed by an almost unendurable craving, for the satisfying of which he is ready to do almost anything, even to commit a crime. There has also been a growing incidence of *heroine snuffing*, which is much more dangerous but presents similar symptoms.

Aside from the intolerable craving, the *symptoms* are far from uniform or definite, but the ultimate general results are the same. The diagnosis, except in later stages, is usually difficult and often impossible; no reliance can be placed on the patient, who has lost all sense of truth and morality. This weakening of moral character is also accompanied by physical effects which may become serious. The most important of these are constipation; loss of appetite; emaciation; contracted pupils; deterioration of skin, hair, and teeth; muscular weakness; tremors; and other nutritional or metabolic disturbances. The victim is also rendered more susceptible to disease and usually succumbs to tuberculosis or pneumonia.

The *treatment*, which must be in an institution or under the close care of one who understands the conditions, consists in withdrawal. There was a time when this was done very gradually, but it is now usually accomplished by very rapid or immediately complete withdrawal. Sometimes the symptoms thus caused become very dangerous, in which case small doses of morphine must be given. The most important of these effects are sudden collapse of the vital functions and severe prostration. Several substances have been suggested to combat the withdrawal effects and the craving. Scopolamine or atropine have been most successful. When the craving has disappeared, which takes place in a few days after the last dose, it is necessary to carry on tonic treatment for weeks and months. Even after this is over, it may be necessary to keep the patient under close observation, and it is doubtful whether any cures are really permanent.

2. Cannabis

Cannabis (Cannabis Indica, Indian Hemp), U.S.P. The dried flowering tops of the pistillate plants of *C. sativa* (*Moraceæ*).

Extract of Cannabis, U.S.P. Dose: 0.015 Gm., ¼ grain, U.S.P.; maximum 1½ grains.

Fluidextract of Cannabis, U.S.P. Dose: 0.1 cc., 1½ minims, U.S.P.; maximum 8 minims.

Tincture of Cannabis, N.F. Dose: 1 cc., 15 minims.

Cannabis has been used in oriental countries since prehistoric times and at present is ingested habitually as an intoxicant by millions of people. As a consequence of this wide usage, the drug is known by a variety of names, the most common of which are hashish, bhang, ganja, and charas. It was formerly supposed that the Indian variety was more potent than others, but since careful investigation demonstrated that this was erroneous, the pharmacopœia allows any source and requires a biological assay. The American-grown hemp, which is referred to as *Cannabis americana*, is identical with *C. indica*. The active principle is a resinous oil, cannabinol, with a very high boiling point.

A therapeutic dose of cannabis gives a peculiar *psychic intoxication*, in which there is dreamy semiconsciousness with varied hallucinations. Ideas are transmitted so erratically that all sense of time and distance disappears. What are thought to be the happenings of a day may take place in a few seconds, and movement to a near object may seem an extraordinarily long journey. The thoughts are generally happy and more or less absurd, but occasionally they involve anxiety or fear. The movements are apparently purposeless and often ridiculous, even to the patient. The sensibility to pain is much lessened, as is also the sense of touch. Ultimately the condition changes to a normal sleep, from which the individual awakens in a few hours, with little or no after-effects except from very large doses. Even with the latter, there is no real danger, as poisoning is very rare.

Cannabis gives rise to a *habit* similar to that from opium and to some tolerance. The continued use of small quantities is almost a universal custom in some eastern countries. It is said that more than 200,000,000 people are addicted. The habit has become a national problem in Brazil, Mexico, and other American states and is spreading into this country. While it is true that many eastern people can use the drug with comparative impunity for years, the white race seems to be very susceptible, and the habitual taking of larger quantities often produces serious mental disturbances or actual insanity. The hashish habit is rightly considered a world menace and every effort to stamp it out should have the earnest cooperation of the pharmaceutical profession.

The variability in strength of different specimens of cannabis has detracted considerably from its therapeutic use, but pharmacopœial requirements for biological standardization may be expected to put this upon a sounder foundation. At present it is *employed* as a hypnotic and analgesic, more efficiently for the former. It certainly has proved decidedly inferior to opium, but the numerous failures to induce sleep might readily be due to insufficient dosage of cannabis which had a low strength. It is also often added to corn remedies, in which it can have no escharotic action on the tissue or in any other way except as a color. The assay given in the pharmacopœia, based upon ability to produce incoordination in dogs, gives satisfactory results.

3. Alcohol

Alcohol (Ethanol), U.S.P., B.P. Not less than 92.3 per cent by weight, corresponding to 94.9 per cent by volume, at 15.56°C., of C_2H_5OH.

Diluted Alcohol, U.S.P., B.P. By weight 41 to 42 per cent, by volume 48.4 to 49.5 per cent. The B.P. describes several dilutions.

Dehydrated Alcohol (Absolute Alcohol), U.S.P., B.P.

Whisky (Spiritus Frumenti), U.S.P.

Brandy (Spiritus Vini Vitis), U.S.P.

Industrial Methylated Spirit, B.P.

On the skin or mucous membrane, alcohol is cooling, because of rapid evaporation, but if this is prevented, there is established a mild irritation which, by continous action, graduates through redness, inflammation, vesication, and even corrosion. These effects are caused by the combined precipitation of protein and abstraction of water. Theoretically, therefore, alcohol should be antiseptic but is so practically only in concentrations that are about 70 per cent; in larger amount it is unable to penetrate the micro-organism.

Alcohol is readily and rapidly *absorbed* from the alimentary tract, regardless of the amount ingested. About 98 per cent is burned to carbon dioxide and water, giving energy equivalent to about 6 calories per cubic centimeter, and the remainder is *excreted* unchanged from the kidneys, lungs, and skin. The oxidation is relatively slow: 8 to 24 hours are generally required for 1 to 2 ounces.

Small doses of alcohol cause a general sense of well-being and an increase of self-esteem, which is evidenced outwardly by talkativeness and boasting. The individual under its influence will attempt impossible tasks and probably feel that he has accomplished them. The face is flushed, the respiration and pulse are temporarily quickened, and the blood pressure rises. When other persons are present, there is also an increased activity and vivacity. With *larger doses* the mental stability is entirely lost, the gait becomes unsteady, and the speech indistinct. Nausea and vomiting are often observed. The individual becomes drowsy and falls to sleep, after which occur unconsciousness and muscular relaxation, soft pulse, lowered temperature, loud breathing, cyanosis, and finally death by respiratory paralysis. It is said that death always occurs if the stupor is prolonged more than 10 to 12 hours. If recovery takes place, the well-known after-effects of depression, vomiting, and headache are experienced.

The *systemic effects* of alcohol have been and are still the subject of extensive debate. One school of investigators has always maintained that the primary result is one of stimulation, while others have held that there is depression from the beginning. More extended experiments have apparently substantiated the latter view, because it has been shown that the psychic effects are probably due to cerebral incoordination and that those upon circulation and respiration are the result of reflex stimulation and environment, not of action upon the nervous or muscular systems. A little alcohol will give for a limited time such stimulation of the respiration, heart, and circulation, but this is of short duration. Experience has long taught that athletes should avoid the drug, even just before a contest, for the depression comes on much too quickly.

Alcohol is *applied locally* for a number of purposes, chiefly for its irritant, astringent, cooling, and solvent effects. Rubbed well into the epidermis, it serves as counter-irritant, being probably the effective agent in several preparations like tincture of arnica and witch-hazel extract. Sponged on the skin, it hardens the tissue to prevent perspiration or possible bedsores and acts as a refrigerant in fevers. It is much used to cleanse the site for hypodermic injection and also disinfects the area. Its irritating action promotes healing when it is applied to ulcers or burns. Sometimes the liquid is injected into nerves to destroy their functions and abolish pain, especially in angina, dysmenorrhea, neuralgia, pruritus, and inoperable cancer.

The need for *internal administration* of alcohol, and the benefits to be derived from such a procedure, have been debated ever since the advent of modern pharmacology and before. While the questions raised have by no means been satisfactorily settled, yet the drug is at present widely employed as reflex stimulant, accessory food, stomachic and digestant, diuretic and diaphoretic, sedative, and hypnotic. There can be no doubt that it temporarily increases the respiration, pulse, and blood pressure, and this may be very useful in cases of shock, fainting, collapse, exhaustion, chills, snake bite, sunstroke, or other emergencies. The subsequent narcosis may aid by removing anxiety and nervousness. The calmative action is also utilized against nervous diseases, insomnia, and melancholy. It is a good hypnotic if the patient is not subject to too much excitement. Kidney irritation and dilation of the cutaneous blood vessels, which follow administration of alcohol, are used to promote diuresis and diaphoresis. For such purposes, it is generally mixed with other drugs, as in tinctures, spirits, etc.

Finally, alcohol is employed as a remedy in *metabolic* and *nutritional diseases* and in conditions of acute inflammation. Under these circumstances the role of alcohol is undoubtedly complex, although there seems no question of the actual benefits in a large majority of the cases. One of the most important factors is its ability to furnish much caloric energy by oxidation, and, since this takes place fairly rapidly and readily, alcohol can replace difficultly digestible food or any food where absorption or digestion has been lessened by disease. Another factor is its narcotic power, which reduces anxiety, promotes rest and sleep, and produces a sense of well-being that may be the one thing needed to establish improvement. In addition, the local irritation serves to increase appetite and promote production of the digestive fluids. The tendency to diaphoresis and diuresis may also play a minor part. The chief conditions under which alcohol is presumed to be valuable are convalescence from infectious diseases, influenza, indigestion characterized by deficiency of ferments, and diabetes. Intravenous injections are sometimes used in pulmonary disorders including pneumonia, diphtheria, septicemia, etc., and have also been applied for general anesthesia.

Acute poisoning by the drug, or drunkenness, is of such common occurrence that the results are well known. The amount which would be toxic seems to vary greatly in different individuals. Children and older persons seem more tolerant to alcohol than to other drugs, and continual use reduces susceptibility. The symptoms may be recorded as follows: sense of comfort and well-being; flushed face; increased activity; impairment of speech, vision, intellect, and gait; vomiting; drowsiness; unconsciousness; weak pulse; slow and noisy breathing; fall of temperature; cyanosis; loss of reflexes. If the coma lasts more than 12 hours, death generally results from respiratory or cardiac paralysis. Should recovery take place, there are headache, neuritic pains, gastritis, diarrhea, and other sequels, which may last for several days. The *treatment* consists in evacuation by a central emetic such as apomorphine and in the administration of symptomatic remedies: soda, stimulants, caffeine, etc.

The importance of alcohol as a poisoning agent, however, rests to a considerable extent on *chronic alcoholism*, which has become a national menace during recent years. The danger of starting such a habit by a therapeutical prescription must always be borne in mind, because the craving and moral depravity induced are similar to those of morphine in a lesser degree. As with cannabis, the continual use of small quantities is probably devoid of any injurious effect; but when the amount is increased, the result may be decidedly dangerous. The chief peril is undoubtedly an increased susceptibility to infection and disease, for the fatalities can almost always be attributed to such complications, rather than to direct action of the poison. The alimentary tract is subject to a chronic catarrh, and there are various degenerative changes in all those organs with which the alcohol comes in contact. There is among alcoholics a great preponderance of mental degeneracy as well as of epilepsy, criminal tendencies, etc. It is, of course, possible that the mental phenomena are causes of the alcoholism and not effects. In any event the ultimate results of intemperate use of the drug are certainly dreadful enough to warrant the extensive campaigns which have been, and are, waged against it.

The *treatment* must be similar to that for morphine or cocaine habits: withdrawal of the drug and a building up of the system by nutritional, hygienic, and dietary measures. The chances for complete cure are not high, but they are much better than are those from other habit-forming drugs.

One frequent sequel of habitual drunkenness is **delirium tremens,** which may be induced by a number of pathological conditions as direct cause. Acute diseases, shock, operations, abrupt withdrawal, overexertion, starvation, or similar circumstances may bring on an attack, or this may result from no traceable cause. The symptoms are trembling, insomnia, excitement, violent delirium, terrifying hallucinations, and dangerous mania. These effects usually wear off in a few days, but they can be mitigated by hypnotics or sedatives. Small doses of alcohol are often advisable to prevent aggravation of the condition occasioned by absence of the accustomed drug.

4. Coal-tar Analgesics

Acetanilid (Antifebrin, Phenylacetamide), U.S.P. Monoacetyl aniline, $C_6H_5NH\cdot COCH_3$. Dose: 0.2 Gm., 3 grains, U.S.P.; maximum 8 grains.

Compound Acetanilid Powder, N.F. Dose: 0.3 Gm., 5 grains.

Tablets of Acetanilid, N.F.

Acetophenetidin (Phenacetin), U.S.P., B.P. Monoacetyl p-amidophenetol, $C_2H_5O\cdot C_6H_4\cdot NH\cdot COCH_3$ 1:4. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 15 grains.

Tablets of Acetophetidine, N.F.

Tablets of Acetophetidine and Phenyl Salicylate, N.F.

Phenetsal (Salophen), N.R. Acetyl p-aminophenyl salicylate. Dose: 0.3 to 1 Gm.

Antipyrine (Phenazone), U.S.P., B.P. Phenyldimethyl pyrazolon, $C_3HON_2(CH_3)_2\cdot C_6H_5$. Dose: as for acetophenetidin.

Melubrin, N.R. Sodium 1-phenyl 2, 3-dimethyl 5-pyrazolon 4-aminomethanesulfonate. Dose: 1 to 2 Gm.

Aminopyrine (Amidopyrine, Pyramidon), U.S.P., N.R. Dimethylaminoantipyrine, $C_3ON_3(CH_3)_4\cdot C_6H_5$. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 15 grains.

Tablets of Aminopyrine, N.F.

Elixir of Aminopyrine, N.F. Dose: 4 cc., 1 fluidrachm.

The coal-tar analgesics are comparatively *recent* additions to our list of medicaments. All of them were produced but a few decades ago as part of the attempts to synthesize quinine or a substance equally valuable in reducing fevers. While the original object was never attained, some of the compounds introduced have proved probably more important than the alkaloid itself, and a better understanding of the relation between chemistry and pharmacology was thus established. Antipyrine was the first to attain prominence, next acetanilid, but acetophenetidin has recently been most popular. The others are comparatively recent.

Aside from an antiseptic and coagulant effect, *local application* of any of them gives little action. The bactericidal power is not usually high but is sufficient to permit their use under certain conditions. There is also some local anesthesia, which may add to the value. All of the compounds are *absorbed* readily from abrasions or mucous membranes. The pyrazolon derivatives are *excreted* unchanged, mainly by the urine, less by the sweat and saliva, and the others are decomposed to paraminophenol, in which form they exert their actions, and which is excreted in the urine as a salt of glycuronic acid.

The *systemic effects* caused by each of these compounds is similar and not well understood. The most important results are reduction of abnormal temperature and a lessening of perception to pain. The analgesia is accomplished without any alteration in the mentality or motor functions and, therefore, is different from that by morphine. Furthermore, it often fails in particular types of pain, making it difficult to trace the mechanism. The antipyresis, which is still more of a problem, has been the subject of several debates. It now seems as if the action must be on the hypothetical heat-regulating center or, more probably, on the control of cutaneous vessels, permitting a dilation and consequent increase in the amount of heat dissipation. Besides these effects, there is always more or less production of methemoglobin, less pronounced with antipyrine, and, with larger doses, a disintegration of the red blood corpuscles, with cyanosis and ultimate collapse. The general circulation is usually not affected, except by toxic doses, which depress the heart and reduce the blood pressure.

All of the compounds are *used* as analgesics in headache tablets and for the relief of neuralgia, rheumatism, and other pains. For this purpose, they are often combined with caffeine, salicylates, or bromides. For the pains of acute infections and many others, they are useless. The doses required for antipyresis are higher and are seldom used, but the drugs are, nevertheless, considered of value in febrile conditions in order to alleviate symptoms. Acetanilid and antipyrine are sometimes ingredients of dusting powders to exert styptic and antiseptic action. Aminopyrine has attained great popularity for its analgesic and antipyretic properties in influenza, rheumatism, measles, colds, and especially in arthritis. Caution must be exercised in any long-continued use, because a certain percentage of persons thus acquire a very serious granulopenia.

The drugs of this group are very apt to cause *untoward side effects*, even with small doses. Acetanilid particularly may cause in many individuals profuse sweating and sudden collapse.

In *poisonous amounts* it produces drowsiness, cyanosis, great reduction in temperature, coldness in the extremities, and dangerous prostration. The pulse becomes weak and irregular, the respiration shallow and labored, the consciousness is partly lost, and death occurs by circulatory failure. In general the symptoms are similar to those from aconite. The *treatment* involves the use of stimulants such as strophanthin, caffeine, and camphor. Antipyrine is less liable to produce the collapse but often gives less dangerous, yet very unpleasant, effects, such as skin eruptions, pain in the mouth and throat, swelling of the eyelids and tears, salivation, or many other peculiar actions. Acetophenetidin is much safer than either, yet it also is liable to produce injurious effects or dangerous poisoning.

5. Trichlorethylene

Trichloroethylene (Trichlorethylene), N.R. $CHCl:CCl_2$. Dose: 15 minims by inhalation; maximum 60 minims a day.

This compound is a solvent which has been administered by inhalation for neuralgia, angina, migraine, and headaches. It has also been suggested as a general anesthetic, but it undoubtedly requires more study.

Antipyretics

The decrease of abnormal temperature is accomplished by increasing heat loss, by lessening heat production, and by secondary action on the nervous system. Heat may be abstracted directly by cold baths and by application of ice packs. The same end result can be attained by any means which causes diaphoresis, best by dilation of the cutaneous vessels or by stimulation of the sweat glands. The vasodilation can be brought about by action on the vasomotor center or by direct depression of the muscles. Decrease of heat production results from any depression of the circulation, as by aconite or veratrum, or it may be induced by suppression of the nitrogenous metabolism, which is apparently the manner in which quinine reduces the temperature. The majority of antipyretics seemingly belong either to the class of vasodilators or to the group which acts upon the hypothetical regulating center. Besides those mentioned above, the list of antipyretics includes such drugs as alcohol, thymol, guaiacol, camphor, cinchophen, digitalis, etc.

Other Analgesics

Any narcotic has a tendency to abolish sensation to pain. The most useful are the anesthetics and many of the hypnotics. In addition, there are many substances, like acetanilid and its allies, which accomplish the result without effect upon other cerebral functions. The salicylates, caffeine, theophylline, cinchophen, and bromides are the most important of this class.

HYPNOTICS

Hypnotics (soporifics, somnifacients) are agents which produce sleep. This is brought about by depression of the psychic centers, preferably without affecting any other portions of the central nervous system. At some stage or other any narcotic will produce sleep, but most of them present too many other effects or danger of poisoning. The ideal hypnotic would be agreeable to take, act promptly and persistently, be free from any depression of the vital functions or from any other than the soporific action, and give no after-effects. Needless to say, none of the present long list exactly, or even nearly, fits these requirements. Morphine, chloral hydrate, barbital, luminal, trional, chloretone, alcohol, and paraldehyde are the most popular.

1. Chloral Derivatives

Chloral Hydrate, U.S.P., B.P. $CCl_3CHO{\cdot}H_2O$. Dose: 0.6 Gm., 10 grains, U.S.P.; maximum 30 grains.

Camphorated Chloral, N.F.

Compound Elixir of Chloral and Potassium Bromide, N.F. Dose: 4 cc., 1 fluidrachm.

Butyl Chloral Hydrate, N.R. $CH_3{\cdot}CHCl{\cdot}CCl_2{\cdot}CHO{\cdot}H_2O$. Dose: 5 to 20 grains.

Chlorobutanol (Chloretone), U.S.P., B.P. $CCl_3{\cdot}C(OH)(CH_3)_2$. Dose: 0.6 Gm., 10 grains, U.S.P.

Chloral hydrate was introduced into medicine as a hypnotic in 1869, being the first of a long list of such drugs. The disagreeable taste and supposed toxicity led later to preparation of numerous derivatives claimed to be improvements. It is doubtful if any of them have any advantage over chloral, and it is certain that, except for morphine, the latter is still the hypnotic most often prescribed and the standard by which others are judged.

Chloral has a *local irritant* action on the skin, which may in concentration be sufficient to cause vesication. On mucous membranes this is apt to be severe unless the drug is largely diluted; and even if this is done, it may cause vomiting.

In *small doses* it causes a feeling of weariness, and a natural-like sleep in about an hour. The patient is readily awakened but, in the absence of external stimuli, remains asleep for several hours, with no after-depression. The heart and respiration are slowed as in normal sleep, and the reflexes are not abolished. *Doses much larger* than those required to produce sleep give a deeper unconsciousness, abolition of the reflexes, dilation of the cutaneous vessels, slowed pulse and respiration, particularly a large fall in blood pressure from vasomotor paralysis, lowering of body temperature, and death by failure of the respiration or sometimes of the circulation.

Chloral hydrate is a reliable *hypnotic* in insomnia due to nervousness, less so when due to pain. It is also efficient as a nervous *sedative* in delirium of fever, seasickness, hiccup, delirium tremens, etc. For relaxing spasm of the cervix in labor, it is presumably effective without decreasing the uterine contraction, also for the convulsive action in tetanus or strychnine poisoning, in this, best supplemented by ether. For the same reasons it is used in asthma, chorea, whooping cough, bladder spasm, or incontinence of urine. *Locally*, chloral hydrate is applied for the relief of rheumatism, toothache, neuralgia, and itching skin diseases. The combinations with camphor or menthol are very popular. **Butyl chloral hydrate** was claimed to be more powerful and less depressing, but it has been shown that it is inferior as a hypnotic although somewhat more analgesic. **Chlorobutanol** is a fairly good local anesthetic and antiseptic and is useful because of these properties as addition to hypodermic solutions. It is readily absorbed and then acts similarly to chloral. Although it is often prescribed in the same conditions as the latter, it is not usually considered so efficient. It has the advantages that it can be injected and in not being irritant.

The *danger* of using chloral, which was formerly considered high, has been shown to be greatly exaggerated. The toxic dose is several times that used in therapy, and the latter is seldom depressant. Occasionally the cutaneous dilation from small amounts gives rise to skin eruptions, but usually there are no side effects not attributable to the local irritant action on the gastric mucosa.

With *poisonous doses,* there will be encountered symptoms of medullary depression as previously described, possibly accompanied by delirium. The effects may take place very rapidly, or the poisoning may be somewhat protracted, but death is rarely delayed more than a few hours. The *treatment* consists in washing out the stomach and then supporting the medullary functions by stimulants. The symptoms and treatment are similar to those for chloroform, but, since the former is much less diffusible, the poisoning lasts longer, and the prognosis is less favorable.

As with all hypnotics, chloral is apt to cause a persistent *habit* and some tolerance, which sometimes becomes very great. The symptoms of chronic poisoning are like those from alcohol, with more tendency to gastric and skin disturbances. As with other habits, treatment is by withdrawal, in this case best gradually.

2. Barbituric Derivatives

Barbital (Barbitone, Veronal), U.S.P., B.P. Diethylbarbituric acid, $CO(NHCO)_2 \cdot C(C_2H_5)_2$. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 15 grains.

Elixir of Barbital, N.F. Dose: 4 cc., 1 fluidrachm.

Tablets of Barbital, N.F.

Soluble Barbital (Barbital Sodium, Medinal), U.S.P., B.P. Dose: as for barbital.

Tablets of Soluble Barbital, N.F.

Phenobarbital (Luminal, Phenylethylmalonylurea), U.S.P., B.P. Phenylethylbarbituric acid, $CO(NHCO)_2 \cdot C(C_2H_5) \cdot C_6H_5$. Dose: 0.03 Gm., ½ grain, U.S.P.; maximum 2 grains.

Soluble Phenobarbital (Luminal Sodium), U.S.P., B.P. Dose: as for phenobarbital.

Elixir of Phenobarbital, N.F. Dose: 4 cc., 1 fluidrachm.

Tablets of Phenobarbital, N.F.

Tablets of Soluble Phenobarbital, N.F.

Amytal, N.R. Isoamylethylbarbituric acid. Dose: 0.02 to 0.6 Gm.

Sodium Amytal, N.R.

Pentobarbital-Sodium, N.R. Sodium ethyl (1-methylbutyl) barbiturate. Dose: 0.1 to 0.4 Gm.

Ipral-sodium, N.R. Sodium ethylisopropylbarbiturate. Dose: 0.12 to 0.25 Gm.

Ipral-calcium, N.R. Dose: as for ipral-sodium.

Neonal, N.R. n-butylethylbarbituric acid. Dose: 0.05 to 0.4 Gm.

Nostal, N.R. Isopropylbromallylbarbituric acid. Dose: 0.05 to 0.3 Gm.

Dial, N.R. Diallylbarbituric acid. Dose: 0.03 to 0.3 Gm.

Ortal-sodium, N.R. Sodium n-hexylethylbarbiturate. Dose: 0.2 to 0.4 Gm.

Alurate, N.R. Allylisopropylbarbituric acid. Dose: 0.06 to 0.13 Gm.

Sodium Alurate, N.R. Dose: as for alurate.

Sandoptal, N.R. Isobutylallylbarbituric acid. Dose: 0.2 to 0.8 Gm.

Phanodorn (Cyclobarbital), N.R. Cyclohexenylethylbarbituric acid. Dose: 0.1 to 0.4 Gm.

Pernoston, N.R. s-butyl β-bromallylbarbituric acid. Dose: 0.2 Gm.

The dialkyl derivatives of barbituric acid were discovered by Fischer in 1903 and introduced into medicine very shortly afterward. Since that time many more have been prepared, but none has been found to possess any great advantage over barbital and phenobarbital. They differ only in dosage required and the margin of safety.

Barbital has no other important *action* than a depression of the psychic centers and approaches as near to the ideal hypnotic as any drug. It is slower than chloral but twice as active; gives no local irritation and no effect on digestion, blood pressure, or respiration; and apparently possesses some analgesic power. Therapeutic doses give, in about ½ hour, a natural sleep which lasts several hours and no after-effect except drowsiness and languor. Larger amounts simply deepen and prolong the sleep, which may culminate in coma and respiratory failure. The margin of safety, however, is quite large. Peculiar reactions are rarely encountered, but more often than with chloral. These are giddiness, headache, nausea and vomiting, diarrhea, skin rashes, fever, and mania.

Barbital is *used* as a hypnotic in simple insomnia and in that of hysteria and from other nervous causes. It is administered in tablets or in powder with much liquid. It is also recommended in delirium tremens, excessive vomiting, seasickness, headache, racking cough, etc. Luminal, which is effective in much smaller doses, and which is very much more toxic, is employed for the same purposes but chiefly as a remedy in epilepsy and other diseases, such as chorea, dysmenorrhea, and exophthalmic goiter. The other barbiturates are similar and used in the same way. Any of them, in the form of salts, can be injected as preliminary to anesthetics or even alone as analgesics or partial anesthetics. All of the derivatives are efficient as antidotes for local anesthetics, strychnine, or picrotoxin.

In spite of the supposed safety, accidents have been experienced from barbital and its derivatives with alarming frequency during recent years, and some states have passed legislative measures to control the sale. The Commonwealth report indicates that there are but 10 groups of poisons more important; barbital occupies a position just below that of strychnine. One of the most significant factors in the *poisoning* is that, although barbital is absorbed readily, the excretion at first goes on very much more slowly, giving rise to *accumulation.* Several days are required to eliminate a single average dose. Other factors are habit formation, small tendency to tolerance, and accessibility to the general public. The accumulative symptoms are general weakness, uncertain movements, anemia, frequent vomiting, constipation, mental dullness, and convulsive spasms.

Acute poisoning by barbital is also becoming more frequent. Even therapeutic doses have been reported to give fatal collapse from peripheral paralysis of the blood vessels. The symptoms from toxic amounts are fall in blood pressure and temperature, shallow breathing, anuria, weakened heart, coma, convulsions, and asphyxia. The treatment would consist in evacuation by the stomach tube or pump and in promoting the elimination by diuretics and purgatives, in the meantime attending to the symptoms of collapse by means of stimulants.

3. Sulfones

Sulfonmethane (Sulfonal), N.F., B.P. Diethylsulfon-dimethylmethane, $(CH_3)_2C(SO_2C_2H_5)_2$. Dose: 0.75 Gm., 12 grains, N.F.; maximum 30 grains.

Sulfonethylmethane (Trional, Methylsulfonal), U.S.P., B.P. Diethylsulfon-methylethylmethane, $(CH_3)(C_2H_5)C(SO_2C_2H_5)_2$. Dose: as above.

The sulfones in therapeutic doses *produce sleep* without any appreciable effect on the circulation or respiration and with little analgesia. There are, however, drowsiness, vertigo, and depression for some hours afterward. Furthermore, the excretion is so slow that dangerous cumulative poisoning is very apt to develop if they are used over too long a period. Large doses give deep narcosis, with slow failure of the vital functions and other less important actions, which are rarely fatal. Recovery has taken place from enormous amounts.

The compounds are *employed* as hypnotics in nervous insomnia and as sedatives in cerebral diseases, hiccup, asthma, and whooping cough, also as remedy for the night sweats of phthisis. They do not irritate the gastric or intestinal mucosa, have no disagreeable taste and few secondary effects, induce no tolerance, and possess a high margin of safety. Contrasted with these are several disadvantages, the chief of which is the danger of poisoning by accumulation. The induction of sleep by sulfonal is very slow, seldom occurring in less than 4 hours and sometimes much later. Trional is much more soluble, giving more rapid action, and is generally preferred.

Acute poisoning by the sulfones is not frequent, but chronic or accumulative poisoning has made their toxicology very important. Large amounts produce profound narcosis and gradual failure of the heart and respiration, which are treated in the usual way by evacuation and stimulation, together with diuresis and purgation. *Continuous administration* over extended periods induces gradually a series of effects which may be fatal. They are lassitude, weakness, nausea, diarrhea or constipation, abdominal tenderness, hematoporphyrinuria, emaciation, mental confusion, skin eruptions, and profound collapse after some time. The most characteristic symptom is the appearance of hematoporphyrin in the urine, which it renders pink. This serves as a warning to withdraw the drug and start treatment, which is even then often too late. Started in time, recovery can generally, but slowly, be accomplished. If the urine has been colored red long, the chances are poor. The best method to avoid poisoning consists in administration for periods of less than a week and then substituting some other hypnotic.

4. Paraldehyde

Paraldehyde (Paracetaldehyde), U.S.P., B.P. $(CH_3CHO)_3$. Dose: 2 cc., 30 minims, U.S.P.

Paraldehyde is similar to chloral hydrate but weaker and much less reliable. Its *physiological action* resembles that of alcohol, with greater prominence of hypnosis and fewer symptoms of excitement. Therapeutic doses give a natural sleep within a short time, and larger doses are relatively safe. It is disagreeable to take, leaves an unpleasant odor on the breath, and is inclined to give gastro-intestinal irritation. Like alcohol, it gives rise to tolerance and habit, with symptoms almost indistinguishable from those of chronic alcoholism.

It is used as a *hypnotic* and *sedative* under the same conditions as chloral. The unpleasant odor and taste have reduced its frequent general employment, for it is certainly safe and fairly reliable. The most useful field is found in the treatment of mental cases, where hypnotics must be given for long periods, and when chloral is contraindicated. It is also administered rectally (15 to 30 cc.) and intravenously (0.2 to 0.3 cc. per kg.) as anesthetic, either alone or with other agents, also as analgesic in labor.

Cases of chronic paraldehyde *poisoning* are more than infrequent, as attested by the Commonwealth report. The symptoms, as has been already pointed out, are like those from alcohol, including the delirium tremens, and are treated in the same way.

5. Scopolamine

Scopolamine Hydrobromide (Hyoscine Hydrobromide), U.S.P., B.P. The hydrobromide of levorotatory scopolamine, $C_{17}H_{21}O_4N$, obtained from plants of the *Solanaceæ*. Dose: 0.0005 Gm., 1/120 grain, U.S.P.; maximum 1/100 grain.

Tablets of Scopolamine Hydrobromide, N.F.

Scopolamine Stable (Scopomannite), N.R.

Scopolamine, or hyoscine, has the same peripheral *actions* as atropine in different degree but differs in its effects on the central nervous system. The mydriasis is much stronger and less prolonged, which may be advantageous in ocular examinations, and the action on secretions is greater. Furthermore, the vagus depression is small and negligible under therapeutic conditions. The chief differences are noted in the central effects, which are sedative and hypnotic and lacking in the characteristic stimulation of atropine. Small doses give, within a few minutes, a natural sleep which lasts for several hours and is followed by dryness of the mouth and throat and some languor. Many individuals, however, do not react in this way and frequently suffer more or less delirium and hallucinations.

Scopolamine is used as a *hypnotic* and *sedative,* especially in those cases in which insomnia is due to motor irritability and to mania. It quiets the reflexes, which is an advantage over morphine, but gives numerous side effects, such as mydriasis and reduction of secretions, and is liable to produce circulatory and respiratory failure, although the margin of safety is theoretically wide. It is usually preferable to atropine or stramonium in parkinsonism. It is also used as a *mydriatic,* being preferred by some to atropine and homatropine. Combined with morphine, it is employed to give *anesthesia* for major operations or to produce partial anesthesia ("twilight sleep") in obstetrics. The disadvantages of such a procedure far outweigh the benefits gained, and it has failed to gain many adherents in this country, but scopolamine is often used for the induction of anesthesia.

Poisoning by scopolamine follows much the same course as that by atropine, with some differences in symptoms. The treatment would be also as for atropine poisoning.

6. Urethane

Ethyl Carbamate (Urethane), N.F. $CO(OC_2H_5)\cdot NH_2$. Dose: 1 Gm., 15 grains.

Urethane is used as an analgesic for laboratory animals, occasionally as a sedative and mild hypnotic for human beings.

Other Hypnotics

Besides the substances described above, there are many others which have hypnotic properties, and a number of these are occasionally prescribed for the purpose. Those unofficial are: amylene hydrate, or tertiary amyl alcohol, used in 15-grain doses; hedonal, a urea derivative, effective after 15 grains; isopral and chloralose, which are similar to chloral; nirvanol (phenylethylhydantoin), which is used in chorea and epilepsy. Of those drugs used chiefly for other purposes, there might be mentioned morphine, cannabis, alcohol, the anesthetics, apomorphine, the bromides, and other so-called sedatives.

SEDATIVES

The sedatives, or calmatives, are a group of drugs which are more or less relics of ancient folk medicine. They are presumed to quiet nerves in hysterical conditions and thus produce an influence favorable to sleep. The value of them is very difficult to determine because of the psychic element, and, if any of them are remedial, it is probably because of this influence. In this connection it is interesting to note that many of the group contain malodorous principles. One might also observe that the list of drugs in this class which are prescribed is steadily growing shorter. The first substances to be described are the bromides, which are true cerebral sedatives and extremely useful; they are in no way to be compared with the drugs which follow.

1. Bromides

Sodium Bromide, U.S.P., B.P. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Sodium Bromide, N.F.

Elixir of Sodium Bromide, N.F. Dose: 4 cc., 1 fluidrachm.

Potassium Bromide, U.S.P., B.P. KBr. Dose: as for sodium bromide.

Elixir of Potassium Bromide, N.F. Dose: 4 cc., 1 fluidrachm.

Ammonium Bromide, U.S.P., B.P. NH_4Br. Dose: as for sodium bromide.

Elixir of Ammonium Bromide, N.F. Dose: 4 cc., 1 fluidrachm.

Calcium Bromide, U.S.P. $CaBr_2$. Dose: as for sodium bromide.

Strontium Bromide, N.F. $SrBr_2{\cdot}6H_2O$. Dose: 1 Gm., 15 grains.

Diluted Hydrobromic Acid, B.P.

Elixir of Three Bromides, N.F. Dose: 4 cc., 1 fluidrachm.

Tablets of Three Bromides (Triple Bromides), N.F.

Elixir of Five Bromides, N.F. Dose: 4 cc., 1 fluidrachm.

Syrup of the Bromides, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Effervescent Salt of Potassium Bromide (Effervescent Potassium Bromide with Caffeine), N.F. Dose: 6 Gm., 90 grains.

Carbromal (Adalin), U.S.P., B.P. Bromdiethylacetylurea, $(C_2H_5)_2$-$CBrCONH{\cdot}CONH_2$. Dose: 0.5 Gm., 8 grains, U.S.P.

Brometone, N.R. Tribrom t-butyl alcohol, $CBr_3{\cdot}COH(CH_3)_2$. Dose: 0.3 Gm. three times a day.

Sabromin (Calbroben), N.R. Calcium dibrombehenate, $Ca(C_{21}H_{41}Br_2$-$COO)_2$. Dose: 0.3 to 1.2 Gm.

Bromural, N.R. 2-bromisovalerylurea, $CH_3{\cdot}CH(CH_3){\cdot}CHBr{\cdot}CO{\cdot}NH$-$CO{\cdot}NH_2$. Dose: 0.3 Gm., three times a day.

The bromides were introduced into medicine about a century ago with the idea that they could replace iodides in the treatment of syphilis and scrofula. It was soon apparent that they are inefficient under such conditions, but at the same time their peculiar narcotic properties were evident, and they have since occupied a prominent place as central sedatives.

The administration of a bromide in therapeutic dose to a healthy person is followed by no noticeable *action*, but larger amounts produce a partial narcosis and muscular relaxation. The psychic and motor centers in the brain are depressed without much effect on that of perception and with none on the medulla or spinal cord. A condition favorable to sleep is thus established, although the bromide is not a hypnotic like morphine or chloral. After smaller amounts the sleep which is induced may be nearly normal, while that following larger doses is not refreshing, since the individual is subject to languor and drowsiness for some time. Very large quantities (10 to 15 grams) give nausea, salivation, headache, confusion in thought and speech, and greatly lowered tone of the reflexes but no sleep for several hours. Acute poisoning, which is very rare, presents the same symptoms to an accentuated degree, followed by profound coma.

The bromides are *employed* as motor and psychic sedatives and as hypnotics. The chief use at present is in the treatment of epilepsy, in which the body must be saturated over long periods of time. The amount required differs in each case and can be determined only by experiment and careful observation. Although the treatment is purely symptomatic and seldom curative, the epileptic attacks disappear or are rendered much milder while the administration is continued. A similar application is made in other convulsive diseases, such as whooping cough, tetanus, strychnine poisoning, and delirium tremens and also in mania and chorea. The bromides are also given to quiet nervous excitement in hysteria, neurasthenia, and cardiac neuroses and as sedatives in seasickness, vomiting of pregnancy, cinchonism, bladder incontinence, excessive sexual excitement, etc. They are not hypnotic but may reinforce the action of barbital or chloral by quieting any condition of excitement.

There is little difference in the effects of *various bromides*, so that the cheaper and more available sodium salt is generally preferred. It also gives less irritation than the older potassium and ammonium salts. Calcium bromide has been claimed superior because of added depression from the metal, but this is unnecessary and may be detrimental. Combinations, as in the triple bromides, are quite popular but with no evidence of added value. During recent years several organic compounds have been introduced with the idea of eliminating the salt action. These are generally less useful, because the bromine is split off too slowly to exert any great effect, unless prolongation is desirable. Where the parent compound already possesses sedative properties, there may be an increase in efficiency, as with the official carbromal.

While acute poisoning by bromides is relatively unimportant, harmful effects are more than frequent. The most common is **bromism,** a peculiar acne, which is often experienced after continued administration of even small doses. Children seem especially susceptible. The eruptions usually disappear upon withdrawal of the drug. When large doses are given over protracted periods, a species of *chronic poisoning* may develop, which is much more serious. It usually presents chiefly degenerative effects on the mentality, together with disturbances of digestion, anemia, emaciation, palpitation, and partial paralysis. The symptoms generally disappear on discontinuing the bromide and injection of chlorides, which facilitate excretion of the slowly eliminated bromide.

2. Valerian

Valerian, U.S.P., B.P. The dried rhizome and roots of *Valeriana officinalis* (*Valerianaceæ*). Dose: 0.75 Gm., 12 grains, U.S.P.

Tincture of Valerian, U.S.P. Dose: 4 cc., 1 fluidrachm.

Ammoniated Tincture of Valerian, N.F., B.P. Dose: 2 cc., 30 minims, N.F.

Fluidextract of Valerian, N.F. Dose: 2 cc., 30 minims.

Extract of Valerian, N.F. Dose: 0.25 Gm., 4 grains.

Acid Ammonium Valerate (Ammonium Valerianate), N.F. Dose: 0.125 Gm., 2 grains.

Elixir of Ammonium Valerate, N.F. Dose: 4 cc., 1 fluidrachm.

Valerian is an ancient remedy for hysteria and was formerly used in England as a perfume. It contains a volatile oil which depends for its odor upon esters of valeric acid. Large doses of the oil, more than are ever used, have been found to depress the central nervous system sufficiently to prevent strychnine convulsions, but average amounts possess no known action except, perhaps, insignificant excitement and high blood pressure. The drug is used, often with bromides, as a sedative and antispasmodic in functional nervous diseases associated with hysteria, as a flavoring agent, and as an adjuvant to tonics. Much of the reputed efficiency under such conditions is probably due to psychic suggestion or to reflexes from the disagreeable odor. The various synthetic esters of valeric acid and the salts are probably useless.

3. Asafetida

Asafetida (Gum Asafetida), U.S.P., B.P. The gum-resin obtained by incising the living rhizomes and roots of *Ferula Assa-fœtida* and *F. fœtida* and of other species of *F.* (*Umbelliferæ*). Dose: 0.4 Gm., 6 grains, U.S.P.

Emulsion of Asafetida (Milk of Asafetida), U.S.P. Dose: 15 cc., 4 fluidrachms.

Pills of Asafetida, N.F.

Tincture of Asafetida, N.F., B.P. Dose: 1 cc., 15 minims, N.F.

As far as is known, asafetida has no physiological action in the doses ordinarily used. Any remedial virtues presumably reside in its odor and taste, which are due to a sulfur-containing oil. It is used largely as a sedative and antispasmodic under the same conditions as valerian and also as an expectorant, flavor, laxative, and carminative. It is sometimes presented in enema to remedy abdominal distention.

4. Sumbul

Sumbul (Musk-root), N.F. The dried rhizome and roots of *Ferula S.*, or of other closely related species of *F.* possessing a characteristic musk-like odor (*Umbelliferæ*). Dose: 2 Gm., 30 grains.

Extract of Sumbul, N.F. Dose: 0.5 Gm., 8 grains.

This drug is very similar to asafetida in properties and employed like it as sedative and antispasmodic in nervous diseases and as carminative.

5. Catnep

Cataria (Catnep, Catmint), N.F. The dried leaves and flowering tops of *Nepeta Cataria* (*Labiatæ*). Dose: 4 Gm., 60 grains.

Elixir of Catnep and Fennel, N.F. Dose: for infants 0.5 cc., 8 minims.

Therapeutically, catnep is very feeble but is sometimes prescribed in the same way as is asafetida.

6. Hop

Humulus (Hop), N.F. The dried strobile of *Humulus Lupulus* (*Moraceæ*) bearing its glandular trichromes. Dose: 2 Gm., 30 grains.

Fluidextract of Hop, N.F. Dose: 2 cc., 30 minims.

Lupulin, N.F. The glandular trichromes of hop. Dose: 0.5 Gm., 8 grains.

Hop contains an aromatic oil and bitter substances, chiefly lupulinic acids. These stimulate and depress the respiratory and vagus centers but have no material action during the administration as usually practiced. The drug has had high reputation as sedative and hypnotic in insomnia and other affections of the nervous system. To induce sleep, a pillow is made of the strobiles. It is also employed as stomachic and sometimes applied as a poultice in inflammations.

7. Celery Seed

Celery Fruit (Apii Fructus, Celery Seed), N.F. The dried ripe fruit of *Apium graveolens* (*Umbelliferæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Celery Fruit, N.F. Dose: 2 cc., 30 minims.

Elixir of Guarana and Celery, N.F. Dose: 8 cc., 2 fluidrachms.

This drug is believed to act as a nerve sedative and is used in hysteroidal states, probably with no advantage. It contains apiol, also found in larger amount in parsley.

Other Sedatives

Most depressant drugs, and many others with no known action, have been used for calming the nervous system. All of those substances described as hypnotics, anesthetics, or analgesics have been called sedatives and are probably better for the purpose than those given above. In addition, the bronchial antispasmodics, like lobelia and conium, are by extension placed in this class. Physostigma, because of its central paralysis and the compounds of zinc, silver, and phosphorus are but a few of the others which have been so called. Mention should also be made of drugs like viburnum and others of the uterine sedative group.

The unofficial list includes musk, skunk cabbage, castoreum, cypripedum, boldo, and solanum.

CENTRAL MOTOR STIMULANTS

1. Strychnine

Nux Vomica (Dog Button), U.S.P., B.P. The dried ripe seed of *Strychnos Nux-vomica* (*Loganiaceæ*). Dose: 0.1 Gm., 1½ grains, U.S.P.; maximum 4 grains.

Powdered Nux Vomica, B.P.

Extract of Nux Vomica, U.S.P., B.P. Dose: 0.015 Gm., ¼ grain, U.S.P.; maximum 1 grain.

Tincture of Nux Vomica, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Fluidextract of Nux Vomica, N.F., B.P. Dose: 0.1 cc., 1½ minims, N.F.; maximum 4 minims.

Strychnine, N.F. An alkaloid, $C_{21}H_{22}O_2N_2$, obtained from nux vomica and from other seeds of the *Loganiaceæ*. Dose: 0.0015 Gm., 1/40 grain, N.F.; maximum 1/10 grain.

Strychnine Nitrate, U.S.P. Dose: 0.002 Gm., 1/30 grain, U.S.P.; maximum 1/10 grain.

Tablets of Strychnine Nitrate, N.F.

Strychnine Sulfate, U.S.P. Dose: as for nitrate.

Tablets of Strychnine Sulfate, N.F.

Strychnine Hydrochloride, B.P.

Solution of Strychnine Hydrochloride, B.P.

Strychnine Phosphate, N.F. Dose: as for nitrate.

Brucine Sulfate, N.F. Sulfate of a second alkaloid, $C_{23}H_{26}O_4N_2$, of nux vomica. Dose: 0.002 Gm., 1/30 grain.

Solution of Nux Vomica Alkaloids, N.F. Dose: 0.5 to 1 cc., 8 to 15 minims for sheep and hogs; 2 to 4 cc., ½ to 1 fluidrachm for horses and cattle.

The *physiological action* of strychnine, and hence of nux vomica, consists chiefly in ascending stimulation and paralysis of the central nervous system. It has a peripheral effect on the motor nerves in man only with large doses, which are generally fatal. The spinal cord, and to a lesser extent the medullary centers, are rendered much more sensitive to external stimuli. The first effects are noted in heightened acuteness of the senses, especially sight, touch, and hearing. Then the muscles become painfully stiff, the breathing becomes labored, the facial contour is distorted, and tetanic convulsions occur. The symptoms of asphyxia are apparent during the attack but relapse during the intermission, becoming more severe each time until death finally takes place from respiratory paralysis. During the early therapeutic stages the blood pressure is raised somewhat, the heart is not affected or is slightly slowed, and the respiratory rate is raised without alteration in the volume. Other systemic effects are of minor importance.

Locally, strychnine in strong solution paralyzes nearly all muscular and nervous tissue, an action which is merely of pharmacological interest. The only local effect of value is its bitter taste, which is extreme; in fact strychnine is probably the most bitter of substances.

The rate of *absorption* varies greatly with the mode of administration, intravenous injections being much more rapid than subcutaneous, which excel the oral route by as much or more. Strychnine is one of the few drugs whose rectal presentation is more effective than by mouth. The absorption is rapid by any mode, and the *excretion* almost as much so, but the effects are, nevertheless, sometimes accumulative, probably because the physiological action outlasts presence of the drug.

Strychnine is *employed* in medicine *chiefly* as a bitter tonic, either in the form of nux vomica preparations or combined with other drugs. The increase in tone of various muscles is at the same time serviceable in cases of "run-down" conditions, such as are encountered in nervous dyspepsia, atonic constipation, convalescence from acute disease, lead poisoning, the debility of chronic alcoholism, and other indefinite circumstances. The combination of bitterness, which increases appetite and digestion, and stimulation of the muscles probably more nearly deserves the title of "tonic" than any of the numerous drug mixtures which are used for the purpose. In paralysis it has often been prescribed but will be of no benefit unless the muscular tissues are unimpaired.

The administration by injection as *stimulant* to the respiration and circulation is often prescribed, in spite of extensive debate as to its justification. It is quite frequently described as respiratory or circulatory stimulant and used in pulmonary disease, shock, asphyxia, poisoning by depressants or anesthetics, fainting, alcoholism, sunstroke, snake bite, etc. The pharmacological evidence appears to show that it could have no possible value to the circulation but that stimulation of the respiration might be of benefit, even if only temporary.

Acute poisoning by strychnine is of considerable importance. The fatal dose is about 0.1 gram or less, but one-tenth of this amount can give toxic effects, while recovery may ensue after more than a gram if prompt treatment is instituted. The symptoms usually start in ½ hour, and death occurs in a few hours; the progress may be considerably influenced by various factors which alter the rapidity of absorption. With small, but toxic, doses there may be only heightened acuteness of the senses, tautening of the muscles, and mild spasms. When large quantities have been absorbed, the victim is often first thrown into a violent convulsion, which apparently involves every muscle of the body. A position is assumed (opisthotonos) in which the trunk is arched and the weight rests on the head and heels, and the jaw is tightly closed, with perhaps foaming at the mouth. During a period which varies from a few seconds to a minute or two, the breathing is suspended, the body remains stiff, and cyanosis develops. Then the muscles begin to relax, and the cyanosis disappears, leaving the patient limp and depressed but perfectly conscious. After a few minutes there is another spasm identical with the first but possibly weaker. The intervals of relaxation grow progressively shorter, and the convulsions weaker, until death from respiratory failure intervenes, generally just after a spasm. Consciousness is retained to the end unless it is abolished by asphyxial coma. The number of attacks is seldom more than four, but there may be as many as eight to ten.

The nature of *treatment* depends upon the stage when it is started. If the poison has just been taken, the stomach should be emptied as rapidly as possible by means of a tube and washed out with permanganate solution. If the poisoning has progressed to the tetanus stage, the administration of ether or chloroform by inhalation must be performed before evacuation can be attempted. Chemical antidotes, best tannic acid or tea, should be introduced into the stomach as rapidly as is consistent with preventing the convulsions. The chief concern, after eliminating the unabsorbed poison, should be to prevent the attacks in order to conserve the strength; the convulsions are not dangerous in themselves. In the later stages artificial respiration is frequently sufficient to save life; in the earlier, ether and chloroform or the barbiturates are almost essential.

Brucine, the second alkaloid of nux vomica, is very similar to strychnine but decidedly weaker. It is used chiefly in veterinary practice.

2. Damiana

Damiana (Turnera), N.F. The dried leaf of *Turnera diffusa* or of *T. aphrodisiaca* (*Turneraceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Damiana, N.F. Dose: 2 cc., 30 minims.

Damiana contains much resin, a bitter principle, and a small amount of volatile oil. It has attained great popular reputation as an aphrodisiac, much of which may be laid to propaganda. It is generally given in combination with other substances as a tonic in sexual impotence, also in forms of brain exhaustion and general paralysis.

SPECIFICS

It has been the endeavor of every generation in the history of medicine to find specific cures for each disease. In spite of the many alleged "discoveries," we are still without any such drugs, even for those afflictions caused by particular organisms, unless we except the vitamins, serums, and vaccines. Quinine in malaria, salicylates in rheumatism, arsphenamine in syphilis, and others are often failures, regardless of the success in many cases. The majority of our drugs, if not all of them, are merely palliative or relieve symptoms only, and this may be of maximum value after all, since nature will generally right itself if properly aided.

THE ANTISYPHILITICS

The treatment of that fearsome disease, syphilis, was attempted in former times by a host of crude drugs, later called alteratives, which were useless. Without any knowledge of the cause, it was discovered that mercury had some influence in remedying syphilis, and for centuries it was used empirically. With the determination that a protozoa, *Treponema pallidum*, is the cause, and with a knowledge of its life history, much progress was made in the way of a rational treatment, but even today the curing of the disease is not uniformly successful. The most approved method involves a combined use of arsenic, bismuth, iodides, and perhaps mercury.

1. Mercury

Mercury (Quicksilver), U.S.P., B.P. Hg.

Mercury with Chalk (Gray Powder), U.S.P., B.P. Dose: laxative 0.25 Gm., 4 grains, U.S.P.; maximum 10 grains.

Mass of Mercury (Blue Mass, Blue Pill, Mercury Pill), U.S.P., B.P. Dose: 0.2 Gm., 3 grains, U.S.P.; maximum 10 grains.

Mild Mercurial Ointment (Diluted Mercurial Ointment, Blue Ointment) U.S.P., B.P.

Injection of Mercury, B.P.

Strong Mercurial Ointment (Mercurial Ointment), U.S.P.

Compound Mercury Ointment, B.P.

Mercurettes, N.R.

Yellow Mercuric Oxide, U.S.P., B.P. HgO.

Yellow Mercuric Oxide Ointment, U.S.P.

Yellow Lotion (Yellow Wash, Yellow Mercurial Lotion, Aqua Phagedænica Flava), N.F.

Compound Yellow Oxide and Adrenalin Ointment, N.R.

Red Mercuric Oxide (Red Precipitate), N.F. HgO.

Ointment of Red Mercuric Oxide, N.F.

Mild Mercurous Chloride (Mercurous Chloride, Calomel, Subchloride or Protochloride of Mercury), U.S.P., B.P. Dose: laxative 0.15 Gm., 2½ grains, U.S.P.; maximum 10 grains.

Compound Pills of Mild Mercurous Chloride (Compound Cathartic Pills, Plummer's Pill), N.F., B.P.

Black Lotion (Black Wash, Black Mercurial Lotion, Aqua Phagedænica Nigra), N.F., B.P.

Ointment of Mild Mercurous Chloride (Prophylactic Ointment, Calomel Ointment), N.F., B.P.

Injection of Mercurous Chloride, B.P.

Tablets of Mild Mercurous Chloride (Calomel Tablets), N.F.

Tablets of Mild Mercurous Chloride and Sodium Bicarbonate, N.F.

Mercury Bichloride (Corrosive Sublimate, Bichloride of Mercury, Corrosive Mercuric Chloride, Perchloride of Mercury), U.S.P., B.P. $HgCl_2$. Dose: 0.004 Gm., 1/15 grain, U.S.P.; maximum ¼ grain.

Poison Tablets of Mercury Bichloride, U.S.P. Large (about 6 grains), small (about 2 grains).

Solution of Mercuric Chloride, B.P.

Yellow Mercurous Iodide (Mercurous Iodide), U.S.P. HgI. Dose: 0.01 Gm., 1/6 grain, U.S.P.; maximum 1 grain.

Tablets of Yellow Mercurous Iodide, N.F.

Red Mercuric Iodide (Mercuric Iodide), N.F., B.P. HgI_2. Dose: 0.004 Gm., 1/15 grain, N.F.; maximum ¼ grain.

Tablets of Red Mercuric Iodide, N.F.

Potassium Mercuric Iodide, N.R.

Ammoniated Mercury (Mercurammonium Chloride, White Precipitate), U.S.P., B.P. $HgNH_2Cl$.

Ointment of Ammoniated Mercury, U.S.P., B.P.

Mercuric Salicylate, U.S.P. Dose: 0.06 Gm., 1 grain intramuscularly twice a week.

Ampuls of Mercuric Salicylate, N.F. Dose: 1 cc. (0.1 Gm.).

Ointment of Mercuric Nitrate (Citrine Ointment), N.F., B.P.

Dilute Mercuric Nitrate Ointment, B.P.

Oleate of Mercury (Oleated Mercury), U.S.P., B.P.

Mercuric Oleate Ointment, B.P.

Mercuric Benzoate, N.R. $Hg(C_6H_5COO)_2 \cdot H_2O$. Dose: 0.015 Gm. intramuscularly every second day.

Mercuric Cyanide, N.R. $Hg(CN)_2$. Dose: as of mercury bichloride.

Mercuric Oxycyanide, B.P., N.R. $Hg(CN)_2 \cdot HgO$. Dose: as of corrosive sublimate.

Mercuric Succinimide, U.S.P. $Hg[N(OCH_2C)_2]_2$. Dose: 0.015 Gm., ¼ grain.

Ampuls of Mercuric Succinimide, N.F. Dose: 1 cc. (0.01 Gm.).

Mercurol (Mercury Nucleinate), N.R. Dose: 0.03 to 0.12 Gm.

Meroxyl, N.R. Chiefly 2, 4-dihydroxy, 3, 5-dihydroxy mercuri-benzophenone 2-sulphonic acid.

Metaphen, N.R. Diacetoxymercuri 4-nitro 2-cresol.

Mercurochrome-220 Soluble, N.R. The disodium salt of 2, 7-dibrom 4-hydroxymercurifluorescein. Dose: 0.23 Gm. per 100 pounds intravenously.

Flumerin, N.R. Disodium 2-hydroxymercurifluorescein. Dose: 0.002 to 0.005 Gm. per kilogram of body weight, intravenously in 2 per cent aqueous solution.

Merbaphen (Novasurol), U.S.P. The double salt of sodium mercurichlorphenyloxyacetate and barbital. Dose: by hypodermic injection 0.15 Gm., 2½ grains.

Merthiolate, N.R. Sodium ethylmercurithiosalicylate, $C_2H_5Hg \cdot S \cdot C_6H_4 \cdot COONa$.

Salyrgan (Mersalyl), N.R. Sodium o-hydroxymercurimethoxypropylcarbamyl phenoxy acetate, $NaOOC \cdot CH_2O \cdot C_6H_4 \cdot CONH \cdot C_3H_5(OCH_3)(HgOH)$. Dose: 0.5 to 2 cc. of 10 per cent solution.

Solution of Colloidal Mercuric Sulfide, N.R. Dose: 2 to 3 cc. intramuscularly.

Mercurin, N.R. A complex mixture of mercurial compounds. Dose: rectally 0.5 Gm. in suppository.

Mercury and its compounds have been used since prehistoric times as agents for the treatment of disease. Even today, after centuries, it is one of the *most valuable* drugs that we possess, indeed almost indispensable. Aside from organic compounds and incidental acid radicals, no element has more compounds in everyday use. All combinations of the element behave alike after absorption and differ only in degree of local action. As a matter of fact, the primary systemic effects are probably the result of a protoplasmic inactivation at different points, qualitatively equivalent to that obtained externally.

The *local action* is typically exhibited by the soluble compounds, such as mercuric chloride, but the insoluble forms produce the same effect to a lesser extent. Even metallic mercury in finely divided condition is no exception. The reaction consists in the precipitation of protein and consequent toxicity to all living cells. When the drug is in high concentration, the tissues are strongly irritated and gradually corroded by destruction of the cells, which may be preceded by vesication. Smaller concentrations or less soluble salts exhibit merely a decreased activity, which is qualitatively identical, and which may give inflammation or, in still more attenuated form, merely irritation. The precipitated compounds combine with materials of the tissues and are transported as such, to give considerable penetration and absorption into the blood. Micro-organisms are also affected, their growth being arrested by dilute solutions, while stronger ones destroy their life. In this respect there is a great difference in the various bacteria, since some of them are very resistant and others are easily killed. Furthermore, the presence of albumin greatly reduces the mercurial action by precipitating the metal.

The rapidity of *absorption* is greatly influenced by several important factors, the chief of which are the site of application and the compound or preparation employed. At least a part of the metal is probably always taken into the system under any circumstances, since it can be found in distant spots after rubbing the insoluble forms on the skin. The salts like calomel, which are very little soluble, are absorbed from the alimentary tract to a small extent but mostly pass through with the feces, after causing an irritant purgation.

Much of the *systemic action* is indefinite and not well understood. The absorbed mercury disappears rapidly from the blood-stream to be deposited in various organs, especially the kidneys and liver, from which it is gradually transported to the channels of excretion. Nearly half of the metal is finally eliminated with the feces, somewhat less than that by the urine, and smaller amounts in the saliva and through other channels. The excretion is so slow that 8 or 10 days may elapse before a single dose is almost eliminated, and traces may remain for months. Wherever the mercury appears, it causes irritation and, in sufficient quantity, inflammation. As would be expected, such effects are noted chiefly in the principal ports of exit, the intestines, mouth, stomach, and kidneys; but the other organs are not immune. The first symptoms of poisoning are salivation and stomatitis. Enormous amounts of saliva may be excreted in a short time. The mercury so excreted finds its way to the stomach, often in sufficient amounts to cause congestion. The colon and cecum and, to a lesser extent, the small intestine are irritated in the same way but much more strongly, causing inflammation, violent purgation, corrosion, and much pain. This may even go far enough to produce perforation of the intestinal wall. Similarly, the mercury, being eliminated by the urinary tract, causes an irritation which excites the kidneys to greater action and may be sufficient to inflame the tubular and glomerular epithelium and finally to destroy the cells. Thus, we experience diuresis at first, with a later tendency to lessened output, containing blood and debris, and eventually anuria. The diuresis is usually inversely proportional to the amount of colonic activity. These three effects—stomatitis, colitis, and nephritis—constitute the chief direct symptoms of acute poisoning.

Small doses of mercury, insufficient to cause the foregoing changes, may have some effects on the metabolism, blood, muscles, and nervous system, but they are probably of minor importance. In case of toxicity, however, these are influenced secondarily in a very profound manner, which will be noted later.

In spite of the simplicity in mode of its action, the *therapeutic uses* of mercury are numerous and varied. The chief ones may be summarized as antisyphilitic, antiseptic, cathartic, antiphlogistic, antiparasitic, diuretic, and cholagogue.

In *syphilis* its efficiency is due to a direct destructive action on the organism, which is superior to that of other drugs. For years there were arguments as to when and how it should be administered, but it was generally agreed that mercury should be presented in some form as early as possible and continued persistently throughout the course of the disease. The introduction of arsenicals and, especially, bismuth has to a great extent supplanted mercury for treatment. Some use a combination of all three by alternation, and, whenever bismuth is contraindicated, mercury is administered intensively. Since a complete discussion of the methods employed is beyond the scope of this volume, it must suffice to say that the aim is to introduce as large a quantity of mercury into the body as the individual will tolerate. This may be accomplished by mouth, by inunction, or preferably by injection into muscular tissue, for which insoluble compounds are best suited, because the action is continued long after the injection. The oral route is usually unsatisfactory on account of the local irritation, but inunction is frequently employed under particular conditions, although the dosage may be uncertain. The salicylate, succinimide, oxycyanide, benzoate, sulfide, and flumerin are most popular for injection.

For *antiseptic* and *antiparasitic* uses, the soluble salts are most highly efficient, within certain limits. Mercuric chloride solution (1:1000 to 1:5000) slowly destroys organisms, or at least renders them inactive, and is often employed to disinfect hands, skin, mucous membranes, wounds, gauze, etc. Ammonium or sodium chloride or tartaric, citric, or hydrochloric acids may be added to facilitate solution and to lessen irritation. A corrosive effect on mental instruments and a strong irritation of abraded surfaces, together with serious danger of poisoning, greatly limit a more extensive use. The double iodide with potassium, the cyanides, mercurol, meroxyl, merthiolate, metaphen, and mercurochrome are applied in the same way, some of them probably being less irritating than the chloride. Mercurochrome, in 1 to 2 per cent solutions, has recently become a very popular substitute for tincture of iodine as a first-aid treatment of cuts and abrasions, but many think it is decidedly inferior. The injection of these mercurials for systemic infections (septicemia, etc.) is sometimes performed, but the evidence for value is not great.

The *insoluble compounds* of mercury are of less value as antiseptics but under certain conditions may be very useful. Calomel undoubtedly serves as an intestinal antiseptic, as evidenced by preventing the decomposition of bile pigment and by diminished indican in the urine. It is also commonly used in the form of ointment to prevent gonorrheal infection. All of the ointments are considered highly in parasitic and other skin diseases, especially in pityriasis, impetigo, and pediculosis.

Any of the insoluble preparations can be administered by mouth to produce *purgation*. Gray powder and blue mass are often used for children, but calomel is usually the agent of choice. It is customary to give a single dose of 2½ grains or to divide this into 10 or 12 portions, giving one every hour, and to follow these with a saline. The result is a dark-green, soft stool in about 6 or 8 hours, with very mild griping. The color of the feces suggests that the mercury increases biliary secretion, and, in spite of substantial evidence that it has no *cholagogue* action, calomel is often administered to stimulate the liver. In larger amounts it gives more or less *diuresis* under varying circumstances, usually also accompanied by salivation and diarrhea. This urinary augmentation is chiefly of value in cardiac dropsies and is to be used cautiously in the presence of renal disease.

Merbaphen and salyrgan are markedly more diuretic than other mercurials and often succeed in bringing about an increase in the urinary output when other agents have failed. Either may be injected intramuscularly or intravenously. They should not be used as routine diuretics but reserved only for those cases in which diuresis is necessary and cannot be attained in other ways. Mercurin is presumed to be useful in this way by rectal injection.

The employment of mercury in the treatment of *acute inflammatory conditions* was extensively practiced some years ago and is still in vogue for a limited number. In ophthalmology the ointments, especially that of the yellow oxide, are applied to reduce swelling and inflammation and to promote the absorption of exudates. In such cases the internal use of iodides at the same time is contraindicated. The ointments are employed likewise as antiphlogistics and sorbefacients for various glandular swellings but are probably less useful for this purpose. In inflammations of serous membranes, such as in pleurisy, carditis, and pneumonia, and in iritis, calomel and other insoluble forms are presented orally. There has been much debate as to the value of this method, and the reduction in its popularity would indicate that the evidence is preponderantly negative.

In any therapeutic use of mercury compounds, the chance for *poisoning* must always be borne in mind. No matter what the position of application and the form of mercury, there is always danger of sufficient absorption to give discomfort, if not actual toxicity. Furthermore, long-continued administration will produce accumulation in the system, and months may be required to secure complete elimination. There are two forms of poisoning, acute and chronic, the first being more important.

Acute poisoning is brought about by large single doses and consists in a violent gastro-enteritis and its secondary effects.

Toxicological statistics show that it is almost always attributable to deliberate or accidental ingestion of mercuric chloride, the fatal dose of which may be placed at 0.5 gram. There are first a disagreeable, metallic taste; a burning pain in the throat, esophagus and stomach; nausea and vomiting, accompanied often by bloody debris from the membranes. In severe cases, these are quickly followed by weak pulse; fall in blood pressure; cold, clammy skin; and other symptoms of collapse; and death may take place within an hour. In case the amount of poison is less, there may be apparent recovery for a day or so, when stomatitis, colitis, and nephritis gradually develop. The urine contains albumin, casts, and then blood and grows smaller in amount. There are bloody diarrhea, abdominal pains, and continual straining at stool. The oral effects begin with salivation and soreness of the gums; then the gums, tongue, and throat become inflamed. The signs of collapse, as already described, make their appearance; the anuria becomes complete; and death follows after a few days from exhaustion or uremia. Very often the effects develop only slowly, with a fatal result in two or three weeks.

Treatment, if begun early, is generally successful, even with enormous doses; but if all of the poison has been absorbed, the prognosis is very unfavorable. Of the various antidotes suggested, eggs and milk are more often available, but tannic acid, charcoal, and calcium sulfide have each been suggested. These should be followed by evacuation, continuous gastric lavage, and enemas to remove the excreted poison. For the remainder, the treatment consists mainly of diet, sanitation, and amelioration of symptoms. The stomatitis is best remedied by carefully cleaning the teeth several times a day and by mouthwashes of potassium chlorate or of hydrogen peroxide. Sodium thiosulfate intravenously and sodium formaldehyde sulfoxylate are employed to promote elimination of mercury and counteract the systemic poisoning.

During therapeutic use of mercury for long periods, there are frequently encountered accumulative symptoms which constitute a *subacute poisoning*. The effects are exactly those encountered secondarily in the acute form, together with some of the nervous and nutritional results of chronic poisoning. A careful prescriber will allow this to proceed only to the point of salivation and some stomatitis and then discontinue for a time.

Chronic poisoning is rare today, except in the industries, where it is difficult to protect the workmen who are handling mercury and its compounds. The effects are caused by prolonged absorption of very minute amounts. They are the stomatitis, dysentery, and renal inflammation of the subacute form, added to effects on the central nervous system and the metabolism. A psychic irritability involving anxiety, restlessness, insomnia, and outbursts of anger, tremor, anemia, and emaciation are most common. There are also degeneration of the bones and often partial muscular paralysis.

2. Iodides

Diluted Hydriodic Acid, U.S.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Syrup of Hydriodic Acid, U.S.P. Dose: 4 cc., 1 fluidrachm.

Sodium Iodide, U.S.P., B.P. NaI. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 30 grains.

Ampuls of Sodium Iodide, N.F. Dose: 10 cc. (1 Gm.).

Potassium Iodide, U.S.P., B.P. KI. Dose: 0.3 Gm., 5 grains; antiluetic 2 Gm., 30 grains, U.S.P.

Solution of Potassium Iodide, N.F. Dose: 0.3 cc., 5 minims.

Tablets of Potassium Iodide, N.F.

Ointment of Potassium Iodide, N.F.

Ammonium Iodide, N.F. NH_4I. Dose: 0.3 Gm., 5 grains.

Tincture of Iodides (Colorless Tincture of Iodine), N.F.

Syrup of Ferrous Iodide, U.S.P., B.P. Dose: 1 cc., 15 minims, U.S.P.; maximum 30 minims.

Pills of Ferrous Iodide, N.F.

Zinc Iodide, N.F. ZnI_2.

Calcium Iodobehenate (Calioben, Sajodin), U.S.P. $Ca(C_{21}H_{42}ICOO)_2$. Dose: 0.5 Gm., 8 grains.

Iodized Oil, U.S.P.

Chiniofon Powder, U.S.P. Chiefly 7-iodo 8-hydroxyquinoline 5-sulfonic acid and its sodium salt. Dose: 1 Gm., 15 grains.

Iodalbin, N.R. A compound of iodine and blood albumin. Dose: 0.3 to 0.6 Gm.

Iodocasein, N.R. A compound of iodine and casein. Dose: 0.3 to 1.3 Gm.

Iodostarine, N.R. Diiodotariric, $C_{18}H_{32}I_2O_2$. Dose as for KI.

Lipoiodine, N.R. Ethyldiiodobrassidate, $C_{21}H_{39}I_2COOC_2H_5$. Dose: 0.3 to 1.8 Gm.

Oridine, N.R. The calcium salt of the iodized fatty acids of cottonseed oil. Dose: 1 gram is equal to 0.28 Gm. of sodium iodide.

Riodine, N.R. A solution in oil of an iodine addition product of castor oil. Dose: 0.4 to 1.2 Gm. per day.

Iothion (Iopropane), N.R. Diiodohydroxypropane, $CH_2I{\cdot}CH(OH){\cdot}CH_2I$.

Siomine, N.R. Methenamine tetraiodide, $(CH_2)_6N_4I_4$. Dose: as for KI.

Iopax, N.R. Sodium 5-iodo 2-pyridon N-acetate, $C_5H_3ION{\cdot}CH_2{\cdot}COONa$. Dose: maximum 30 Gm. intravenously.

Neo-iopax, N.R. Disodium N-methyl 3, 5-diiodo 4-pyridoxyl 2, 6 dicarboxylate, $NaOOC{\cdot}C_5ONI_2(CH_3)COONa$. Dose: 15 Gm. intravenously.

Vioform, N.R. Iodochlorhydroxyquinoline, $C_9H_4NIClOH$. Dose: 0.25 Gm. four times a day with great caution.

Lipiodol, N.R. Iodized poppy-seed oil 40 per cent.

Lipiodol Radiologique Ascendant, N.R. 10 per cent.

Chloriodized Rapeseed Oil, N.R.

Stearodine, N.R. Calcium iodostearate. Dose: 0.01 Gm.

Diodrast, N.R. 3, 5-diiodo 4-pyridon N-acetic acid with diethanolamine. Dose: 7 Gm. intravenously.

Hippuran, N.R. Sodium o-iodohippurate. Dose: 12 Gm. intravenously or orally.

Skiodan (Methiodal), N.R. Sodium iodomethanesulfonate. Dose: 20 to 40 Gm. intravenously.

Although iodides are among the oldest and most useful of drugs, we know little about their mode of action. Long before iodine was discovered, and the salts known, crude drugs containing the element were employed empirically in tuberculosis and scrofula. The salts were introduced nearly a hundred years ago in the treatment of syphilis and, at various times, for other diseases. The evidence for their peculiar value is almost entirely clinical.

The alkali iodides are very easily *absorbed* from all mucous membranes and from abraded surfaces; transported to various parts of the body, including most secretions; and rapidly *excreted.* A single dose of potassium iodide has been known to appear in the urine in less than 2 minutes, while 5 to 8 minutes is the usual time required. They are excreted mainly by the urine but also appear in the saliva, tears, perspiration, etc. A small amount is generally retained by the thyroid gland, but the majority is eliminated in large part within 24 hours, the remainder more slowly for another day.

During this brief stay in the body, the only important *physiological action* that can be demonstrated is osmosis. Strong solutions are irritating to mucous membranes because they are hypertonic. After they are absorbed, the iodides cause an increase in many of the secretions, including urine, bronchial mucus, tears, and sweat, an action typically saline, but the iodides seem particularly active in this respect. Furthermore, they are said to increase menstruation, but large doses decrease the secretion of milk.

The most important *use* of iodides in medicine is as palliative in secondary and tertiary syphilis. The results are often very brilliant, especially in inducing the absorption from gummatous ulcers and in promoting their healing. For this purpose sodium or potassium iodide is sometimes given in doses as high as 20 grams daily. Although they are not curative and have no influence on the organisms or on the Wassermann reaction, the iodides seem to assist materially the effectiveness of mercury. The explanation for their value is not known in spite of many theories, but whatever evidence we have would seem to indicate that they alter the cell walls of blood vessels in some way, increasing the permeability and promoting the absorption of cellular exudates. The formation of a proteolytic enzyme has also been suggested.

The iodides are also employed with frequent success in inflammatory and circulatory diseases, where the action is probably similar to that in syphilis. Chronic rheumatism, chronic bronchitis, hardening of the arteries, angina pectoris, gout, scrofula, hypertension, neuralgia, and asthma are the principal conditions of this kind. The iodides are used in exophthalmic goiter, particularly as a preparation for operation.

The iodides are of remarkable benefit in many cases of *simple goiter*. The normal thyroid gland takes up iodine from the blood and converts it into several compounds, the ultimate product being the official thyroxin. Whenever there is a deficiency of the element in the food, the output of thyroxin is decreased, and there may be an enlargement of the gland as in goiter. In fact it is claimed that practically all thyroid swellings in persons under thirty years of age are due to deficiency of iodine. On this basis the iodides are administered in small amounts to reduce the goiter or prevent it. Remarkable success was attained in 1918 by treating thousands of school children in certain communities, in which this disease is particularly prevalent. They are given twice a year 0.2 gram per day for 10 days. On the other hand, when the goiter is due to tumor or other disease, the drugs may be decidedly harmful, particularly in persons who are old enough to acquire a malignant gland. For this reason, many authorities have cautioned against the promiscuous administration of iodides in goiter, especially deprecating the present wide use of commercial table salt which has been iodized.

The property of *increasing secretions* is also utilized. The potassium salt, particularly, is frequently prescribed to increase that of the bronchi and render it more liquid. Any of them will promote diuresis, but other salines, which are not so liable to cause poisoning, are generally preferred. The sodium salt, which is less irritating, has been employed to accelerate elimination of heavy metals in case of poisoning, chiefly from lead and mercury. Finally, the iodides are useful in testing kidney functioning and to determine if a prescribed medicine has been actually taken, since tests for iodides in the urine are easily made.

Decided disadvantages in the use of these compounds are the appearance of poisonous symptoms known as *iodism* and the irritation of alimentary mucosa. Although the latter can be readily guarded against, the former is all too common and apparently not preventable without foregoing the therapeutic value. The appearance of poisonous symptoms may follow the administration of a small dose, or it may be the result of continuous medication, and sometimes smaller amounts seem more harmful than larger ones. The effects are evidently dependent on the individual, perhaps being influenced by differences in pathological conditions. The manifestations of iodism also are variable, and each of those mentioned may occur singly or combined with the others. Those most often met are irritations of the oral and respiratory mucous membranes, giving simulation of the common cold. These may extend to the eyes and to the frontal sinus to give violent headache. Pulmonary edema, pleurisy, laryngitis, stomatitis, and other more serious results are encountered, and they may even be fatal.

Later effects are skin rashes and interference with metabolism, probably referable in large measure to thyroid changes and to the catarrh. The dermal changes are of various forms to imitate almost every known skin disease, including boils, urticaria, eczema, etc. Anemia, loss of appetite, emaciation, nervousness, insomnia, palpitation, and other nervous and metabolic disturbances are usually encountered after continued administration. Upon withdrawal of the drug, there is an immediate tendency to recovery, but this may be very slow.

The *organic combinations* of iodine have been produced in large number to replace iodides for systemic effects. They are designed to obviate the salt action on oral administration, to prevent any iodism, and to make absorption and excretion slower, so as to retain physiological effects for a longer time. It is possible that some of them accomplish each one of these objects but probably at the expense of remedial merit. The clinical evidence is far from being conclusive, and most authorities still favor the inorganic iodides, which are unquestionably superior, or at least equal, in therapeutic efficiency. Other organic iodides (thymol iodide) were designed as substitutes for iodoform.

Since iodine in any form is impervious to X-ray, many of the organic combinations have been introduced for the purpose of making contrast pictures of the bladder, urethra, gall bladder, etc. The iodized oils are injected into the cavity in question, while the water-soluble preparations are given orally or injected intravenously. The most useful of the latter class are iopax, neo-iopax, and iodophthalein (*q.v.*).

3. Arsenic

Arsenic Trioxide (Arsenous Acid, Arsenous Oxide, Arsenous Anhydride, Arsenic, White Arsenic), U.S.P., B.P. As_2O_3. Dose: 0.002 Gm., 1/30 grain, U.S.P.; maximum 1/10 grain.

Tablets of Arsenic Trioxide, N.F.

Solution of Arsenous Acid (Hydrochloric Solution of Arsenic, Solution of Arsenic Chloride), U.S.P. Dose: 0.2 cc., 3 minims, U.S.P.; maximum 10 minims.

Solution of Potassium Arsenite (Fowler's Solution, Arsenical Solution), U.S.P., B.P. Dose: as for solution of arsenous acid.

Arsenic Triiodide (Arsenous Iodide), U.S.P., B.P. AsI_3. Dose: 0.005 Gm., 1/12 grain, U.S.P.; maximum 1/5 grain.

Solution of Arsenic and Mercuric Iodides (Donovan's Solution), N.F., B.P. Dose: 0.1 cc., 1½ minims, N.F.; maximum 10 minims.

Sodium Cacodylate, U.S.P. $Na(CH_3)_2AsO_2$. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 2 grains.

Ampuls of Sodium Cacodylate, N.F. Dose: 1 cc. (about 0.3 Gm.).

Exsiccated Sodium Arsenate (Anhydrous Sodium Arsenate), N.F. Dose: 0.003 Gm., $\frac{1}{20}$ grain.

Solution of Sodium Arsenate, N.F. Dose: 0.2 cc., 3 minims.

Solarson (Solution of Chlorarsenol), N.R. A 1 per cent solution of ammonium heptenchlorarsonate, $CH_3(CH_2)_4CCl{:}CH{\cdot}AsO(OH)ONH_4$, in saline. Dose: 1 to 2 cc. intramuscularly or subcutaneously.

Acetarsone (Stovarsol), N.R. 3-Acetylamino 4-hydroxyphenyl 1-arsonic acid, $HO(CH_3CONH)C_6H_3{\cdot}AsO(OH)_2$. Dose: 0.25 Gm. orally two or three times a day for a week.

Arsphenamine (Salvarsan, Arsenobenzol, Diarsenol), U.S.P., N.R. Diaminodihydroxyarsenobenzene hydrochloride, $HCl{\cdot}NH_2OH{\cdot}C_6H_3As{:}AsC_6H_3\text{-}OHNH_2HCl{\cdot}2H_2O$. Dose: Caution! intravenous, 0.4 Gm., 6 grains, U.S.P.

Silver Arsphenamine (Silver Salvarsan, Sodium Silver Arsphenamine), N.R. Dose: 0.1 to 0.3 Gm. intravenously or intramuscularly.

Solution of Arsphenamine, N.R.

Neoarsphenamine (Neosalvarsan, Neodiarsenol, Novarsenobenzol), U.S.P., B.P. Chiefly sodium 3-diamino 4-dihydroxyarsenobenzene methanal sulfoxylate, $NH_2OH{\cdot}C_6H_3As{:}AsC_6H_3OH{\cdot}NH(CH_2O)OSNa$. Dose: Caution! intravenous, 0.6 Gm., 10 grains, U.S.P.

Sulpharsphenamine (Sulfarsenol), N.R., B.P. Disodium 3,3′-diamino 4,4′-dihydroxyarsenobenzene N-dimethylenesulfonate, $NaOSO_2CH_2NH\text{-}(OH)C_6H_3As{:}AsC_6H_3NHOH{\cdot}CH_2SO_2ONa$. Dose: maximum 0.4 to 0.5 Gm. by any hypodermic route.

Tryparsamide, U.S.P. Sodium N-phenylglycinamide p-arsonate, $NH_2{\cdot}\text{-}CO{\cdot}CH_2{\cdot}NH{\cdot}C_6H_4AsO(OH)ONa{\cdot}\frac{1}{2}H_2O$. Dose: Caution! intravenous 2 Gm., 30 grains.

Bismarsen (Sulpharsphenamine Bismuth), N.R. The sodium salt of a bismuth derivative of sulpharsphenamine. Dose: 0.1 to 0.2 gram intramuscularly.

Mapharsen, N.R. The hemialcoholate of 3-amino 4-hydroxy phenylarsine oxide hydrochloride, $HCl{\cdot}(NH_2){\cdot}C_6H_3(OH)AsO{\cdot}\frac{1}{2}C_2H_5OH$. Dose: 0.03 to 0.06 Gm. intravenously.

Carbarsone, N.R. p-carbamido-phenylarsonic acid, $NH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}\text{-}As{:}O(OH)_2$. Dose: 0.25 Gm. orally twice a day.

The element arsenic has been of *great importance* to man for centuries, because of its widespread occurrence and its high medicinal value. Nearly all ores, and hence many metalliferous products, contain varying amounts, ranging from traces to several per cent. Many soils furnish it to plants and then to animals. It has been demonstrated as a constant component of man and most other animals in minute amounts. The quantity in human beings is probably less than 1 milligram, chiefly in the thyroid gland. Arsenic compounds have important actions on the metabolism and on the course of disease, and relatively larger amounts are actively poisonous. The former difficulty of detecting the element led to a wide use in criminal practice; indeed, arsenic was at one time much the most important poison. With improved knowledge of its properties and easy methods of identifying, the toxicological importance has waned somewhat but is still high because of accidental absorption in industry, on account of a wider use in medicine, and because it is still commonly employed for suicidal or homicidal purposes.

The compounds of arsenic which are used in medicine are divided sharply into *two groups.* The inorganic derivatives are very active as poisons and give numerous effects which can be utilized for the treatment of disease. In the fight against blood parasites, however, they are too toxic to the host, so that effective destruction of the organism is impossible. The organic arsenicals, on the other hand, have a minimum action on the human body, without losing the qualities inimical to the parasites. The Ehrlich theory, which has been devised to explain the difference on the ground of affinities for various groups, is rather elaborate, based upon pure speculation, and really unnecessary. We shall consider the organic combinations separately, because they are used for an entirely different purpose.

Applied locally, arsenic compounds give a mild and prolonged corrosive action. They do not precipitate albumin and give little irritation but destroy the tissues slowly upon prolonged contact. On mucous membranes or wound surfaces they induce inflammation with considerable pain and, ultimately, an extensive necrosis.

Absorption takes place readily from almost any surface; less, but in minute amounts, from the intact skin. The arsenic rapidly disappears from the blood-stream to be deposited in all tissues of the body, chiefly in the kidneys, liver, spleen, and heart. From here it is slowly and incompletely *excreted* by all channels, mostly in the urine after hypodermic administration and in the feces after oral ingestion. A single dose may remain in the body for as much as 10 days, and, after repeated doses, 2 to 4 months may elapse after the final dose before the elimination is anywhere near completion; traces have been found in the hair and skin months after excretion has ceased.

The *systemic action* of arsenic consists chiefly in capillary paralysis, which induces circulatory, alimentary, and renal changes; a probable depression of certain muscles; and reputed stimulation of metabolism. Small doses were found by older investigators to have an improving effect on growth and nutrition, increasing appetite and weight and giving greater inclination to work, as well as promoting the skin nutrition and the production of subcutaneous fat. More recent experiments have failed to confirm the results and indicate that any benefits must be minute. Practically all significant effects from therapeutic amounts can be attributed to a paralysis of capillary muscles and the resultant increase in permeability of the walls, occurring chiefly in the alimentary tract and kidneys. The mucous membranes of the stomach and intestines become swollen and congested, hemorrhages may appear, and fatty infiltration of the gland cells often results. There is accumulation of thin fluid within the tract, with more or less violent diarrhea. In fact the symptoms are identical with those of cholera. A similar effect is also noted in the kidneys, where the glomerular capillaries are enlarged sufficiently to decrease production of urine and finally to stop it entirely. The blood pressure falls markedly with higher doses, owing to this capillary dilation and a direct depressant effect upon the cardiac muscle. The nervous system is probably unaffected by arsenic, except secondarily from the alimentary and renal actions. Large doses cause death by respiratory paralysis, which is brought about by exhaustion from gastro-enteritis. The compounds in which arsenic is trivalent are much more active, both medicinally and in poisoning, than are those in which the element is pentavalent.

Tolerance to arsenic is certainly not an established fact, although there is no unanimity of authorities on the subject. In various parts of the world, notably in Styria and the Tyrol, the natives begin taking the element when young, as a stimulant, and habitually ingest it in ever increasing quantities to a ripe old age. Some of them consume as much as a gram per week without any apparent ill effects. Experience with most other individuals, however, would indicate that such a tolerance cannot be generally established and, even if so, surely cannot be high.

The *therapeutic uses of inorganic arsenic* are almost entirely empirical and bear no relation to the known physiological action. The pharmacology may sometimes explain a particular application but generally is inadequate. Nevertheless, the benefits derived in certain conditions are well established by years of practical experience. Arsenous acid is used as a caustic in superficial cancer of the skin and to destroy the tissue in decayed teeth, methods rapidly being displaced by more modern ones. Small doses may be beneficial in atonic conditions by increasing appetite and promoting nutrition. The arsenic compounds have long been employed in malaria, as an adjunct to quinine in acute cases and for their tonic properties in the poor nutrition of chronic stages. They are prescribed in neuralgia, bronchitis, asthma, chorea, chronic rheumatism, arthritis, the cachexia of tuberculosis, chlorosis, pernicious anemia, leukemia, and rickets. The benefits are sometimes very brilliant, often only temporary, and more often fail to materialize at all. Practically all non-parasitic skin diseases are treated by oral administration of arsenicals, frequently with excellent results, and hair growth is presumed to be improved in the same manner, a fact which is sometimes utilized in veterinary practice to produce an elegant appearance in the fur of animals. Finally, the inorganic derivatives are still sometimes employed in syphilis, although preference is usually given to the organic forms.

Large doses of any arsenic compound give rise to *acute poisoning*. Death may take place very rapidly from collapse due to the wide capillary paralysis. In most instances, after about ½ hour, there are a feeling of dryness in the throat, difficulty in swallowing, vomiting, and painful diarrhea, sometimes accompanied by blood and mucus. The output of urine is diminished or almost ceases and may contain blood and albumin. The choleric diarrhea, which is almost incessant, becomes of watery consistency only. The withdrawal of enormous quantities of fluid gives rise to great dryness of all other tissues, with hoarseness and difficulty in speaking. After a few hours, there ensue vertigo, muscular cramps, and cyanosis, possible fainting. Death may occur after a short coma, or it may be preceded by convulsions. The end takes place generally about 48 hours after onset, and, if it is delayed for a longer period, there are further symptoms as experienced in therapeutic poisoning. These consist in stomatitis, laryngitis, conjunctivitis, and inflammation at various other points, together with polyneuritis and skin disturbances. Should recovery take place, the patient is very liable to endure symptoms of chronic poisoning and is sometimes subject to more or less permanent paralysis.

The *treatment*, to be of aid, must be prompt. The stomach should be emptied by a tube and washed out repeatedly with warm water. If the tube is not available, an emetic such as apomorphine may be used. The official arsenic antidote precipitates the poison, but the resultant magma is almost as readily absorbed as the original and must itself be removed, so that it is practically useless. Sodium thiosulfate is said to be an excellent antidote when injected intravenously. The symptoms of collapse can be treated with stimulants, such as caffeine and digitalis.

Chronic poisoning arises from the ingestion of small quantities over long periods or may be a sequel of the acute form. The sources of the arsenic, when not due to medicinal use, are very numerous, as could be expected in view of its wide occurrence. Wallpaper, cosmetics, water supplies, furs, dyed cloth, minerals, fruits after arsenical spraying, and kitchen utensils are but a few of the many common articles which often contain appreciable amounts of the element. Recently there has been considerable agitation against American fruit which has been sprayed with lead arsenate, but stricter government control has minimized the danger. The symptoms are varied and may persist for months and years, even after withdrawal of the source. For the most part they resemble closely those of chronic lead poisoning, with greater tendency to local effusions and disturbances of sensation and less muscular paralysis. The subject is important, but a full discussion is unrelated to the purposes of this volume. The student is referred to Peterson and Haines or to some other text on toxicology.

The Organic Compounds.—Inorganic arsenic is very poisonous to many plants and lower animals as well as to the vertebrates. This applies in particular to many pathological protozoa but not to all. There are also other notable exceptions to a universal toxicity, such as varieties of mold which seem to thrive on arsenic. While that of malaria is quite resistant, the parasites which cause syphilis, relapsing fever, sleeping sickness (trypanosomiasis), and other protozoan infections are more or less susceptible. It would be logical, therefore, to use the drug in maximum dose to destroy or drive out such organisms from the blood. Attempts to do this have been made for years, using Donovan's and Fowler's solutions, but clinical experience shows that, when arsenic is administered thus in sufficient amounts to be at all effective, it is very poisonous to tissues of the host. In attempts to produce compounds which would have minimum toxicity to man with efficient parasiticide qualities, some thousand arsenicals have been prepared, and several valuable ones introduced into medicine.

The *use of these compounds* depends upon the gradual liberation of simple arsenic combinations, in which the element is trivalent. Since some of them have a low action on the body tissues without loss of efficiency, it is presumed that these have particular affinity for the parasites. This is more or less confirmed by the fact that, after administration, arsenic can be found in parts infested with disease and not in other regions. Some of the earlier substances, including sodium cacodylate, contain arsenic in pentavalent form, and it is assumed that these are first reduced. They are generally less useful and, if the change to lower valence is rapid, may give ordinary arsenical poisoning; the cacodylates may also give a very foul odor to the breath and excretions. The arsphenamines are used intramuscularly or, better, intravenously not only for syphilis but also for all sorts of protozoan infections and even as a substitute for inorganic arsenic, in various conditions in which the latter is employed. One useful application is locally and parenterally for trench mouth. The technic of injection must be rigid and carefully followed, or serious results may be produced, but since this is not a part of the pharmacist's province, a full discussion would be out of place. Tryparsamide apparently has a special value in African sleeping sickness and in cerebrospinal syphilis. Solarson and the cacodylates are recommended merely as substitutes for inorganic arsenic; acetarsone and carbarsone orally in the treatment of amebic dysentery and trench mouth. None of them is efficient in infections of the blood by protozoa.

The injection of organic arsenic often produces *toxicity* which is of various kinds. The causes are ascribed differently by authorities and probably in many cases consist in faulty technic or poor quality of the preparation. In a small number of injections there are immediate febrile reactions, which are relatively unimportant and may be idiosyncrasies. After an hour or so, or even later, there may be commonly a second series of reactions, consisting of fever, swollen tongue and lips, cyanosis, vomiting, and diarrhea. These effects, which are not often dangerous and recede after a few hours, are attributed to several causes, of which the most logical appears to be a specific reaction on the tissues or organism at the site of disease. Infrequently there is a later severe, and even fatal, toxicity, which may be of several types. In one there may be cyanosis, weakness, convulsions, and coma; less usual are symptoms of jaundice or severe skin disease. One of the untoward effects so frequently encountered is atrophy of the optic nerve, leading to blindness, but this is more often a sequel after arsenilic acid derivatives than after the arsphenamines. The whole subject of poisonous effects from organic arsenicals has given rise to a voluminous literature. for which the student is referred to a more extensive text.

4. Bismuth

Bismuth Subnitrate (Bismuth), U.S.P., B.P. A basic mixture yielding not less than 79 per cent of bismuth oxide. Dose: 1 Gm., 15 grains, U.S.P.

Tablets of Bismuth Subnitrate, N.F.

Paste of Bismuth (Beck's Bismuth Paste), N.F.

Bismuth Subcarbonate, U.S.P., B.P. A basic mixture yielding not less than 90 per cent of bismuth oxide. Dose: as for subnitrate.

Tablets of Bismuth Subcarbonate, N.F.

Magma of Bismuth (Milk of Bismuth), N.F. Dose: 4 cc., 1 fluidrachm.

Cremo-Bismuth, N.R. Dose: 4 to 15 cc.

Lac Bismo, N.R. Dose: 4 to 15 cc.

Compound Lozenge of Bismuth, B.P.

Precipitated Bismuth, B.P.

Bismuth Subgallate (Dermatol), U.S.P. A basic mixture yielding 52 to 57 per cent bismuth oxide. Dose: as for subnitrate.

Tablets of Bismuth Subgallate, N.F.

Bismuth Subsalicylate, U.S.P., B.P. A basic mixture yielding 62 to 66 per cent bismuth oxide. Dose: orally 1 Gm., 15 grains; parenterally 0.125 Gm., 2 grains, U.S.P.

Ampuls of Bismuth Subsalicylate, N.F. Dose: 1 cc. (0.1 Gm.).

Injection of Bismuth Salicylate, B.P.

Bismuth and Potassium Tartrate, U.S.P. Dose: parenterally 0.15 Gm., 2½ grains.

Bismuth Sodium Tartrate, N.R. Dose: intramuscularly 0.03 Gm.

Glycerite of Bismuth, N.F.

Elixir of Bismuth, N.F. Dose: 4 cc., 1 fluidrachm.

Injection of Bismuth, B.P.

Sodium Potassium Bismuthyl Tartrate, N.R.

Bismosol (Solution of Sodium Potassium Bismuthyl Tartrate), N.R. Dose: parenterally 1 cc. (0.1 Gm.).

Bismuth Betanaphthol (Orphol), N.R.

Bismuth Tribromphenate (Xeroform), N.R. Dose: 1 to 3 Gm.

Mesurol (Benzobis), N.R. Basic bismuth methoxy hydroxy benzoate. Dose: 1 cc. of 20 per cent emulsion intramuscularly.

Biliposol, N.R. A complex compound combining α-carboxethyl β-methyl nonoic acid. Dose: 2 cc. intramuscularly.

Bismo-Cymol, N.R. A basic salt of camphor 3-carboxylic acid. Dose: intramuscularly to represent 0.1 Gm. of bismuth.

Oleo-Bi, N.R. Chiefly bismuth oleate in suspension. Dose: intramuscularly 2 cc., representing 0.1 Gm. of bismuth.

Thio-Bismol, N.R. Sodium bismuth thioglycollate chiefly. Dose: intramuscularly 0.2 Gm.

Quinine Bismuth Iodide, N.R. Of varying composition.

Quiniobine, N.R. A solution of quinine bismuth iodide in olive oil. Dose: 1 to 2 cc. intramuscularly.

Tartro-Quiniobine, N.R. A suspension of quinine bismuth iodide and sodium potassium bismuthyl tartrate in olive oil. Dose: as quiniobine.

Sodium Iodobismuthite (Sodium Bismuth Iodide), N.R.

Iodobismitol with Saligenin, N.R. A solution of sodium iodobismuthite and sodium iodide in 1,2-propylene glycol containing saligenin and a small amount of acetic acid. Dose: intramuscularly 2 cc.

Insoluble compounds of bismuth are applied externally and internally as *inert, insoluble powders* to inflamed or irritated surfaces. It is claimed that enough is dissolved by the body fluids to give astringent and antiseptic effects; and while the amount of solution must be very small, this gives bismuth salts a decided advantage over others of the class. In the alimentary tract they are employed to check diarrhea and vomiting and in any condition of irritation, such as ulcers or foreign bodies. For diarrhea they are generally mixed with an intestinal antiseptic, such as salol. Externally they are used as dusting powders on abraded parts, drying up the excretions and forming a crust, which is equivalent to a scab and under which healing quickly takes place. The bismuth compounds are opaque to the X-ray and have been employed for diagnostic examinations. For all practical, protective purposes, there is no advantage of any one bismuth compound, but the *subnitrate* and *subcarbonate* are older and *usually selected.* Although the subcarbonate can neutralize some acid and is occasionally employed as antacid, the subnitrate is devoid of any such property, in spite of an impression to the contrary.

Large doses of bismuth do not ordinarily produce any *harmful effects* when administration takes place by mouth. Occasionally, however, poisoning has occurred in such cases and also from the application too freely to wounds or burns or after injection into confined areas, as into sinuses. With the subnitrate, the symptoms may be those of nitrites formed by reduction, cyanosis, respiratory distress, and collapse. True bismuth poisoning is characterized by a dark line on the gums, similar to that from lead; salivation; diarrhea; nephritis; headache; and albuminuria. Withdrawal of the drug usually constitutes a cure. Injected directly into the blood-stream, bismuth may give rise to symptoms similar to those from arsenic, with an especially rapid fall in blood pressure.

During recent years, compounds of bismuth have replaced, partly or entirely, those of mercury in the fight against syphilis and some similar infectious diseases. Indeed, today practically every course of treatment for syphilis involves administration of bismuth in some form. Together with iodides, bismuth and arsenic constitute the present means of attack, although mercury and bismuth are often alternated. Unlike mercury, bismuth is given only by intramuscular injection, usually the salicylate or one of the tartrates. Symptoms of poisoning, chiefly skin lesions or a dark line on the gums, are indications to stop the bismuth and to substitute other drugs temporarily.

ALTERATIVES

These are remedies formerly defined as substances which alter the course of morbid conditions in some indefinite way. It can thus be seen that the term was probably used to conceal ignorance as to the manner of action. According to the definition, any drug could be viewed as belonging to the class, since the improvement or alteration of disease is the primary purpose of medicine. As a matter of fact, however, the old alteratives were presumed to exert their favorable action on the general metabolism or nutrition. They were commonly employed in those diseases which were mysteries or for which no other drugs had been found.

The most important of this group were arsenic, iron, mercury, and the iodides, but it also contained hundreds of others. As the developments of modern science threw more light on drug action, and the mechanics of many substances was explained, they were transferred to other classes, while others were found useless and abandoned. The surviving substances are of considerably less importance than formerly, by many considered absolutely useless, and the conditions for their employment are very indefinite. Since the chief value was once considered as evidenced in syphilis and rheumatism, they are described here.

1. Sarsaparilla

Sarsaparilla, U.S.P. The dried root of *Smilax medica*, known in commerce as Mexican Sarsaparilla; or of *S. officinalis*, or of an undetermined species of *S.*, known in commerce as Honduras Sarsaparailla; or of *S. ornata*, known in commerce as Central American or Jamaica Sarsaparilla (*Liliaceæ*).

Fluidextract of Sarsaparilla, U.S.P. Dose: 2 cc., 30 minims.
Compound Syrup of Sarsaparilla, U.S.P. Dose: 15 cc., 4 fluidrachms.
Compound Fluidextract of Sarsaparilla, N.F. Dose: 2 cc., 30 minims.

The root contains several glucosides of the saponin group which are unabsorbed and, therefore, non-toxic. No other physiological action could be expected from the drug but a local irritation of the gastro-intestinal tract, with nausea and diarrhea. It has been, and is still, prescribed as an alterative in chronic skin diseases, rheumatism, syphilis, etc. Just as is the case with so many "blood medicines," it is administered in conglomerate mixture, usually with stillingia, guaiac, and xanthoxylum.

2. Trifolium

Trifolium (Red Clover Blossoms), N.F. The dried inflorescence of *T. pratense* (*Leguminosæ*). Dose: 4 Gm., 60 grains.

Fluidextract of Trifolium, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Fluidextract of Trifolium, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Syrup of Trifolium, N.F. Dose: 8 cc., 2 fluidrachms.

Trifolium has no medicinal virtues at all, as far as investigation has shown, but it is used as an alterative or "blood purifier," usually mixed with other drugs. It is sometimes smoked in antiasthmatic powders.

3. Echinacea

Echinacea (Niggerhead, Sampson-root), N.F. The dried rhizome and roots of *Brauneria pallida* or of *B. angustifolia* (*Compositæ*). Dose: 1 Gm., 15 grains.

Fluidextract of Echinacea, N.F. Dose: 1 cc., 15 minims.

This is an eclectic remedy for boils, skin diseases, cancer, and other infectious maladies. It is also credited with being locally and systemically analgesic, but no evidence has ever been forthcoming to show that it has any virtue whatever.

4. Guaiac

Guaiac (Guaiac Resin), N.F. The resin of the wood of *Guaiacum officinale* or of *G. sanctum* (*Zygophyllaceæ*). Dose: 1 Gm., 15 grains.

Tincture of Guaiac, N.F. Dose: 4 cc., 1 fluidrachm.

Ammoniated Tincture of Guaiac, N.F. Dose: 2 cc., 30 minims.

Guaiac was formerly, like sarsaparilla, a very popular alterative in chronic rheumatism, syphilis, uterine disorders, acute infections, and tuberculosis. In small doses it can be taken over long periods with impunity, but in larger amounts it is a purgative, and any virtues that it has probably must be ascribed to the latter action. Occasionally it is used in the form of gargle or troche in the local treatment of diseased conditions of the mouth and throat.

5. Phytolacca

Phytolacca (Poke Root), N.F. The dried root of *P. americana* (*Phytolaccaceæ*). Dose: emetic 1 Gm., 15 grains; alterative 0.1 Gm., 1½ grains.

Fluidextract of Phytolacca, N.F. Dose: emetic 1 cc., 15 minims; alterative 0.1 cc., 1½ minims.

This drug is a local irritant and probably depressant to the central nervous system. It has been used by the eclectics as an emetic and purgative and especially as an alterative in dermatology, rheumatism, syphilis, cancer, etc. It is sometimes applied locally in the treatment of parasitic and other skin diseases.

6. Stillingia

Stillingia (Queen's Root), N.F. The dried root of *S. sylvatica* (*Euphorbiaceæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Stillingia, N.F. Dose: 2 cc., 30 minims.

Stillingia is a common ingredient of alterative mixtures for syphilitic and rheumatic conditions. Aside from emetic and purgative action, it is probably inactive.

7. Xanthoxylum

Xanthoxylum (Prickly Ash Bark), N.F. The dried bark of *Zanthoxylum americanum,* known in commerce as Northern Prickly Ash Bark, or of *Z. Clava-Herculis,* known in commerce as Southern Prickly Ash Bark (Rutaceæ). Dose: 2 Gm., 30 grains.

Fluidextract of Xanthoxylum, N.F. Dose: 2 cc., 30 minims.

Prickly Ash Berry (Xanthoxyli Fructus), N.F. Dose: 1 Gm., 15 grains.

Xanthoxylum, being locally irritating and bitter, is employed as stomachic and carminative, as a corrective in conditions of the mouth and throat, and in toothache. It is sometimes applied like mezereum as a counter-irritant. The principal reputation, however, is in chronic rheumatism and in general as alterative, usually mixed with drugs like sarsaparilla and hydrastis.

8. Burdock

Lappa (Burdock Root), N.F. The dried, first-year root of *Arctium L.* or of *A. minus* (*Compositæ*). Dose: 2 Gm., 30 grains.

Fluidextract of Lappa, N.F. Dose: 2 cc., 30 minims.

Burdock root has been used and recommended as an alterative in the various conditions for which such substance is considered efficacious, especially in skin diseases, where it is applied locally and given internally. There is no evidence whatever that it is of any value.

9. Aralia

Aralia (American Spikenard, Spignet), N.F. The dried rhizome and roots of *A. racemosa* (*Araliaceæ*). Dose: 2 Gm., 30 grains.

Aralia is used in domestic medicine in a manner similar to sarsaparilla, which it resembles in appearance. Its presence in cough mixtures would appear to indicate a reputation as expectorant.

10. Corydalis

Corydalis (Turkey Corn, Squirrel Corn), N.F. The dried tuber of *Dicentra canadensis* or *D. Cucullaria* (*Fumariaceæ*). Dose: 0.6 Gm., 10 grains.

Corydalis contains several alkaloids, chiefly corydaline or bulbocapnine. It is an eclectic alterative and tonic, used with other drugs in syphilis, scrofula, skin diseases, and rheumatism.

11. Cascara Amarga

Cascara Amarga (Honduras Bark), N.F. The dried bark of *Sweetia panamensis* (*Leguminosae*). Dose: 1 Gm., 15 grains.

The bark contains a bitter alkaloid but is without physiological action in the doses used. It is a common addition to alterative mixtures, being contained in trifolium official preparations.

12. Elder Flowers

Sambucus (Elder Flowers), N.F. The air-dried flower of *S. canadensis* or of *S. nigra* (*Caprifoliaceæ*). Dose: 4 Gm., 60 grains.

Sambucus was formerly much used as an alterative in rheumatism and syphilis but is practically abandoned today, except an an ingredient of stillingia preparations. It is probably mildly diaphoretic and, in large doses, emetic and cathartic.

Other Alteratives

Out of the hundreds of drugs which have been described as alteratives, mention can only be made of a few which are still sometimes so prescribed. These include most of the stomachics, mezereum, ichthyol, baptisia, sabal, thuja, conium, boldo, sulfur, damiana, dulcamara, marrubium, fucus, yeast, manaca, tonga, and guaiacol.

ANTIMALARIALS

The antimalarials or antiperiodics were formerly quite numerous, but the group now comprises very few substances. Cinchona or quinine is generally efficient as prophylactic or curative of malaria, relapsing fever, or other periodically recurring diseases. In cases which resist them, plasmochin, arsenic, methylene blue, or antimony may be selected. Most of the alteratives have been so used.

1. Quinine

Cinchona (Peruvian Bark, Red Cinchona Bark, Calisaya), U.S.P., B.P. The dried bark of the stem or of the root of *C. succirubra* or its hybrids, known in commerce as Red Cinchona, or of *C. Ledgeriana*, *C. Calisaya* or hybrids of these with other species of *C.*, known in commerce as Calisaya Bark or as Yellow Cinchona (*Rubiaceæ*). Dose: 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Fluidextract of Cinchona, B.P.

Extract of Cinchona, B.P.

Tincture of Cinchona, B.P.

Compound Tincture of Cinchona, U.S.P., B.P. Dose: 4 cc., 1 fluidrachm, U.S.P.

Quinine, U.S.P. An alkaloid, $C_{20}H_{24}O_2N_2 \cdot 3H_2O$, obtained from cinchona. Dose: 1 Gm., 15 grains, U.S.P.; maximum 15 grains.

Ammoniated Solution of Quinine, B.P.

Quinine Sulfate, U.S.P., B.P. Dose: as for quinine, U.S.P.

Tablets of Quinine Sulfate, N.F.

Quinine Bisulfate, U.S.P. Dose: as for quinine.

Quinine Tannate, B.P.

Quinine Dihydrochloride, U.S.P., B.P. Dose: as for quinine.

Ampuls of Quinine Dihydrochloride, N.F. Dose: 1 cc. (0.5 Gm.).

Quinine Hydrobromide, N.F. Dose: 0.3 Gm., 5 grains, N.F.

Quinine Hydrochloride, N.F., B.P. Dose: 0.3 Gm., 5 grains, N.F.

Ampuls of Quinine Hydrochloride and Ethyl Carbamate, N.F.

Quinine and Urea Hydrochloride, U.S.P. Dose: hypodermic 1 Gm., 15 grains in single dose daily.

Ampuls of Quinine and Urea Hydrochloride, N.F. Dose: 1 cc. (0.5 Gm.).

Quinine Ethyl Carbonate (Euquinine), U.S.P., B.P. Dose: as for quinine.

Quinine Phosphate, N.F. Dose: 0.3 Gm., 5 grains.

Quinine Salicylate, N.F. Dose: 0.3 Gm., 5 grains.

Totaquine, B.P. Mixture of the alkaloids from cinchona.

Coco-Quinine, N.R.

Elixir of Cinchona Alkaloids, N.F. Dose: 8 cc., 2 fluidrachms.

Cinchonidine Sulfate, N.F. The sulfate of an alkaloid, $C_{19}H_{22}ON_2$, obtained from cinchona. Dose: 0.15 Gm., 2½ grains, U.S.P.; maximum 20 grains.

Cinchonine Sulfate, N.F. The sulfate of an alkaloid, $C_{19}H_{22}ON_2$, obtained from cinchona. Dose: as for cinchonidine sulfate.

Quinidine Sulfate, U.S.P., B.P. The sulfate of an alkaloid, $C_{20}H_{24}O_2N_2$, from cinchona. Dose: 0.2 Gm., 3 grains, four times a day, U.S.P.; maximum 10 grains.

Ethylhydrocupreine Hydrochloride (Optochin), U.S.P. $C_{21}H_{28}O_2N_2 \cdot HCl$.

Of the 30 or more alkaloids in cinchona bark, the principal ones are the 4 official bases. It is believed that the physiological action of all is represented by that of quinine, present in the largest amount, but there is little evidence of experimental work to substantiate this. The action of quinine will be described, and the minor differences of the others pointed out, as far as they are known.

Practically all of the effects of quinine are attributable to a *destructive action on protoplasm,* which is especially strong on lower forms of life. The action begins with a temporary, but quickly disappearing, stimulation of cellular activity, followed by sluggishness and, eventually, permanent inactivation of the protoplasm. Concentrations of 0.05 per cent inhibit the growth of bacteria, and stronger solutions kill them. The presence of pus or serum apparently is without influence in reducing this effect. Ameba, yeasts, leucocytes, spermatozoa, and other low forms of life are affected in the same way. Applied locally to various parts of the body, there is a similar but smaller action on tissue. Muscles particularly are rendered weaker and more easily fatigued, and higher concentrations may kill the fibers and lead to sloughing. The sensory nerves are paralyzed in the same way to give local anesthesia which is very lasting, but which may result in permanent injury to the cells and ultimate edema and sloughing. Unstriped muscles are uniformly stimulated by direct contact and, to a much smaller extent, by oral or hypodermic administration. This is especially true of the uterus, intestines, spleen, and bronchi.

Quinine is *absorbed* readily from the alimentary canal, mainly in the small intestine. It is transported by the blood, presumably in a peculiar combination with the corpuscles; is largely destroyed; and the balance *excreted* chiefly in the urine. A single oral dose begins to appear in the urine in a very short time, but the amount becomes progressively smaller and does not usually cease for two or three days. The total so eliminated is about one-third of the amount given, the balance being mostly destroyed, since very little is found in other secretions. If the drug is injected subcutaneously, it is deposited locally and but slowly absorbed.

The physiological *action after absorption* is apparently still due to destruction or inactivation of protoplasm. Unstriped muscles are incited to greater contraction, but seemingly large doses are required to secure sufficient concentration. The uterus especially is stimulated during labor, less so when virgin or in normal pregnancy. The heart is generally slowed and weakened by direct action on the cardiac muscle, and a fall in blood pressure results from large doses. The nerve trunks are comparatively immune from quinine, and no important effects are noted here, except in case of poisoning. The temperature is not altered if normal and very little if high, except in malaria, where specific destruction of parasites causes reduction of the fever. There are also no great changes in the metabolism, except a decrease in nitrogenous output and those following the local action. Quinidine is similar to quinine but much more powerful in its effects on the heart. Cinchonidine resembles these in every way, giving also a stimulation of the spinal cord which leads to convulsions. Cinchonine has a like action, although it is much less powerful.

Unusual reactions from quinine are rather common. They generally take the form of effects often observed after large doses. Derangements of hearing and sight, with sometimes total deafness or blindness, are not rare, and in some cases these may be permanent. Skin eruptions, nausea, vomiting, diarrhea, abortion, or reduction in the number of leucocytes may be noted. It is interesting to observe that susceptibility to quinine can readily be determined by local reaction on the abraded skin of 0.1 per cent solutions.

The *chief therapeutic use* is for the treatment of malaria and other periodic diseases, in which the alkaloid appears to be specifically inimical to the causative organisms. These invade the red corpuscles and periodically swarm to other cells, at the same time producing a high fever. A single large dose of quinine will usually stop an attack, but in order to destroy all of the protozoa, it is necessary to continue the administration over extended periods. The quinine is almost always given by mouth, but if it gives too much discomfort or vomiting, if the digestion is disturbed too much, or if the patient is abnormally susceptible, the soluble salts may be injected intramuscularly or intravenously. The tannate or euquinine has a less disagreeable taste.

The *other uses* of quinine are quite varied in character. Because it is presumed to reduce the size of enlarged spleen in malaria, it has been given in other splenic diseases characterized by this condition. Other fevers, such as those of colds and influenza, are treated with it, not only to reduce temperature but also to give analgesia and because of its antiseptic action. The efficiency is never very high in most cases, but occasionally it is markedly successful in reducing the temperature. On account of the idiosyncrasies, and because of the frequent appearances of toxic symptoms, the employment of quinine under such circumstances is much less popular than formerly. It is still a common addition to cold tablets.

Quinine has *also been administered* as an analgesic in headache and neuralgia, although aspirin and the coal-tar antipyretics are now preferred. It has been recommended in whooping cough, hiccup, and asthma, in which excellent results have sometimes been reported. In cholera and amebic dysentery it has been given by mouth and by high rectal injection and similarly as a treatment for threadworms. Irregularities of the heart are often remedied by quinine, and more particularly by quinidine, which has attained great popularity in auricular fibrillation during the last few years, in spite of numerous accidents. Massive doses are given in pneumonia, with the claim that the symptoms are relieved and the duration shortened. Quinine has a high reputation as uterine stimulant, for which purpose it is used at all stages of labor, to restore menstrual flow, and to induce abortion. Expert opinion, however, asserts that uterine contractions are never started by the drug and, therefore, that it can never produce abortion.

Locally, quinine is injected, in the form of a soluble salt like the double one with urea, to produce local anesthesia and to sclerose varicose veins and hemorrhoids. The preliminary irritation and tendency to tissue destruction are great disadvantages, but the effect is very lasting, sometimes for two or three days. For the same purpose, the sulfate is dusted on wounds, where it exerts also an antiseptic, styptic, and stimulating action, and is used as a local application for relaxed sore throat, hay fever, trachoma, keratitis, and hemorrhoids. Solutions are sometimes injected for gonorrhea or other urinary infections and as anthelmintic for pinworms. They are also given orally in amebiasis, colitis, skin diseases, etc. A suppository of quinine is an excellent purgative in constipation. Quinine salts are frequently added to hair tonics.

One of the principal applications in therapy is as a *stomachic tonic.* For this purpose the cinchona preparations are probably preferable, but quinine mixtures are common. The alkaloid is intensely bitter, being in this respect as powerful as any other, but in addition it is presumed to be generally tonic to the metabolism. It is pertinent to note, however, that the crude drug is usually combined with nux vomica; that the alkaloid is given with iron, arsenic, and strychnine; and that alcohol represents a large portion of any such prescription. Any other bitter would probably accomplish as much under the circumstances.

The *toxicology* of quinine is not very important. Large doses produce mental confusion and uncertain gait, ringing in the ears, deafness, visual disturbances, and somnolence. This symptom-complex, which is known as *cinchonism,* is also observed after other drugs, such as the salicylates. In more extreme cases, unconsciousness, delirium, coma, and possibly convulsions may occur. Fatalities are rarely encountered, usually the result of attempted abortion or, in susceptible persons, of therapeutic overdoses. It is said that bromides will greatly mitigate the symptoms of cinchonism, which explains their common prescription with quinine.

In this connection should be mentioned the persistent view that old solutions or preparations of quinine become toxic by transformation to **quinotoxine**, more aptly named **quinicine.** That the latter can readily be formed from quinine is not doubted, because any acid can bring about the change in a short time, but it has been definitely shown that quinicine is not more poisonous. Such an old preparation may lack the virtues attributable to quinine, but it cannot be more toxic.

Ethylhydrocupreine is used like quinine in pneumonia but most often as a local treatment of certain eye diseases, particularly if the pneumococcus is present. Quinidine is employed in various heart diseases and as an efficient substitute for quinine in malaria. Cinchonine and cinchonidine are similar to the others in every respect, but they are much weaker and not often used.

2. Plasmochin

Plasmochin is said to be ethylamino 6-methoxy quinoline. The drug is very effective against the gametes of malaria, less so in other stages. It is now used (10 to 30 milligrams) in combination with quinine, by some being considered indispensable. In addition, plasmochin can be applied to the treatment of blackwater fever, where quinine is contraindicated. **Atabrine** is another synthetic employed similarly.

4. Phlorhizin

Phlorhizin (Phlorizin), N.R. A glucoside, $C_{21}H_{24}O_{10}\cdot 2H_2O$, obtained from the root of the apple, pear, and other fruit trees. Dose: 0.3 to 0.6 Gm., 5 to 10 grains.

Phlorhizin destroys malarial parasites in a test tube and has been employed internally to combat the disease. It invariably produces a glycosuria and, in larger doses, injures the kidneys, so that the clinical application in malaria should be abandoned. The prompt appearance (15 to 30 minutes) of glucose in the urine after hypodermic administration has been utilized as a test of renal functioning.

ANTIRHEUMATICS

1. Salicylates

Salicylic Acid, U.S.P., B.P. $C_6H_4(OH)COOH$ 1:2.
Compound Salicylic Collodion, N.F.
Salicylic Acid Ointment, B.P.

Sodium Salicylate, U.S.P., B.P. $NaC_7H_5O_3$. Dose: 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Elixir of Sodium Salicylate, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Elixir of Sodium Salicylate, N.F. Dose: 4 cc., 1 fluidrachm.

Ampuls of Sodium Salicylate, N.F. Dose: 5 cc. (1 Gm.).

Ammonium Salicylate, U.S.P. $NH_4C_7H_5O_3$. Dose: 1 Gm., 15 grains, U.S.P.; maximum 30 grains.

Strontium Salicylate, N.F. $Sr(C_7H_5O_3)_2{\cdot}2H_2O$. Dose: 1 Gm., 15 grains, N.F.; maximum 30 grains.

Salicin, N.F., B.P. A glucoside, $C_{13}H_{18}O_6$, obtained from several species of *Salix* and *Populus* (*Salicaceæ*). Dose: 1 Gm., 15 grains, N.F.; maximum 30 grains.

Methyl Salicylate, U.S.P., B.P. $C_6H_4(OH)COOCH_3$, obtained synthetically or by distillation from the leaves of *Gaultheria procumbens* (*Ericaceæ*) or from the bark of *Betula lenta* (*Betulaceæ*). Dose: 0.75 cc., 12 minims, U.S.P.; maximum 30 minims.

Wintergreen Water, N.F.

Acetylsalicylic Acid (Aspirin), U.S.P., B.P. $C_6H_4(OCOCH_3)COOH$ 1:2. Dose: 0.3 Gm., 5 grains, U.S.P.; maximum 20 grains.

Tablets of Acetylsalicylic Acid, N.F.

Compound Paste of Acetylsalicylic Acid, N.F.

Novaspirin (Salicitrin, Methylene-citryl Salicylic Acid), N.R. $HOOC\text{-}(C_6H_4)OOC{\cdot}CH_2C(OCH_2OCO)CH_2COOC_6H_4COOH$. Dose: 1 Gm. several times daily.

Ethyl Salicylate (Sal-ethyl), N.R. $C_2H_5OOC{\cdot}C_6H_4OH$. Dose: 0.3 to 0.6 cc. three or four times a day.

Mesotan (Salmester), N.R. $CH_3OCH_2OOC{\cdot}C_6H_4OH$.

Spirosal (Glysal), N.R. Monoglycol salicylate, $HOCH_2CH_2OOC\text{-}C_6H_4OH$.

Sal-ethyl Carbonate, N.R. The carbonic ester of ethyl salicylate. Dose: 0.3 to 1 Gm. three or four times a day.

The *physiological action* of salicylates is the same for all of the compounds, but there are quantitative differences. The acid is markedly irritating to mucous membranes and abraded surfaces and on the skin produces a gradual destruction of tissue without pain, actions which prevent its internal administration. It is about equal to phenol in antiseptic power and has the advantage of not being volatile. The salts are scarcely irritating to any surface and not greatly antiseptic, but oral ingestion is followed by liberation of some free acid in the stomach and in the urine, if acid, producing weakly germicidal quality and some irritation. All of the compounds are rapidly *absorbed* from the alimentary tract, and the more volatile penetrate the skin more or less readily. They are transported by the blood as sodium salt and *excreted* within 48 hours unchanged or as conjugated compounds, chiefly in the urine but somewhat in the milk, perspiration, and bile. Except for osmotic action, therapeutic doses have no significant effects on normal persons, but idiosyncrasies to the drugs are fairly common, consisting of the usual effects with small amounts or tolerance to large quantities. When the temperature is high, it is promptly reduced to normal by an increase of heat loss and by dilation of the cutaneous vessels, accompanied by sweating. When certain forms of pain exist, they are dulled or abolished by salicylates. The excretion of nitrogen and sulfur is greatly increased, but it is not known if this is accompanied by a larger amount of basal metabolism. The alkaline reserve is said to be decreased because of respiratory stimulation.

Larger doses of salicylates give rise to *cinchonism,* or a series of symptoms resembling those from quinine. They start with a feeling of stuffiness in the head, ringing in the ears, headache, mental confusion, and dizziness. If the effects become more severe, there are nausea and vomiting from central action and also sweating, deafness, partial blindness, nephritis, and sometimes delirium and skin eruptions. These conditions are seldom dangerous and disappear when the drug is discontinued. In fatal cases there is a rapid collapse and asphyxia, with final arrest of the respiration.

Salicylic acid is *applied locally* in itching skin diseases, either as ointment or as dusting powder. It is often also employed to prepare antiseptic dressings, although the irritation caused on abraded surfaces generally is objectionable. Application to corns and warts gives softening of the tissue and permits its easy removal. Used as a dusting powder, it is considered valuable to prevent excessive perspiration. The common addition of minimum quantities of salicylates to foods as preservative is probably not harmful. Sodium salicylate is probably as useful as any agent for a sclerosing medium.

The salts are *employed chiefly in rheumatic fever,* or inflammatory rheumatism, in which they are almost specific. The pain and inflammation rapidly disappear, the high temperature promptly becomes normal, and the general comfort of the patient improves in every way. It is a debated question, however, whether or not the duration of the disease is shortened, and it is probable that salicylates act mostly on the symptoms. Various attempts have been made to explain this action on the basis of antipyresis, of analgesia, or on account of increased uric acid excretion, but the fact seems to remain that other drugs, which are as good or better under such circumstances, are greatly inferior in the treatment of inflammatory rheumatism. Although any of the salicylates is effective, the sodium salt is most commonly used, at first in large doses (1 to 2 grams), the amount being reduced as the symptoms abate. The effectiveness and reduction in toxicity are greatly enhanced by simultaneous administration of bicarbonates.

In other forms of rheumatism and in *other fevers or pains*, the salicylates are often employed. In gout, sciatica, chronic rheumatism, lumbago, arthritis, chorea minor, pneumonia, typhus, influenza, etc., sodium salicylate may often lessen the pain and discomfort. Acetylsalicylic acid is an almost universal cure for headaches, but much of its reputation with the laity is psychological, and it is certain that antipyrine and phenacetin are more efficient in some cases. In certain types of pain, such as that after extraction of a tooth or after tonsillectomy, aspirin is probably unsurpassed except by morphine. The pains of neuralgia, neuritis, etc., are treated in the same way.

The salicylates are supposed to promote the absorption of edematous fluids, especially in pleurisy. The mechanism is unknown, because diuresis could certainly not explain it. They are *also used* to increase biliary flow, but, although they seem to have a very minor action in this respect, the bile salts are certainly much more efficient. Occasionally the salts are given to exert an antiseptic effect in the intestinal or urinary tract, an application for which phenyl salicylate is usually preferred. The diaphoresis, which is characteristic of larger doses, is sometimes utilized in the treatment of dropsies. Salicin is employed infrequently as a stomachic. The esters of salicylic acid are designed to obviate the gastro-intestinal and other untoward effects and have no other advantage. Spirosal is administered by inunction, while mesotan is used as a counter-irritant, particularly in rheumatic conditions. Methyl salicylate is a very common flavoring agent.

2. Cinchophen

Cinchophen (Phenylcinchoninic Acid, Atophan), N.F., B.P. C_6H_5-$C_9H_5N{\cdot}COOH$. Dose: 0.5 Gm., 8 grains, N.F.; maximum 15 grains.

Tablets of Cinchophen, N.F.

Chloroxyl (Cinchophen Hydrochloride), N.R. Dose: as for cinchophen.

Neocinchophen (Tolysin), U.S.P. Ethyl ester of 6-methyl cinchophen, $CH_3(C_6H_5)C_9H_4N{\cdot}COOC_2H_5$. Dose: 0.5 Gm., 8 grains.

All three of these compounds have a *similar action,* but neocinchophen is practically tasteless, while the others are bitter. They cause a large increase in the amount of uric acid excretion and a simultaneous decrease in the amount held in the blood, without affecting the total quantity formed by the protein metabolism. The salicylates accomplish the same result but less powerfully. The action from a single dose of cinchophen lasts about 9 or 10 hours, when the normal uric acid level is restored. There is no evidence of any influence on urate deposits, but claims are made that the calculi of gout are reduced in size. Other products of metabolism are altered to a lesser extent, ammonia, total nitrogen, etc. Large doses are usually well tolerated, but occasionally there may be digestive disturbances, skin diseases, and circulatory effects.

Cinchophen was introduced into medicine on the basis that reduction in the blood content of uric acid would be *curative in gout.* It was found of great value in relieving the pain of acute forms but less in chronic gout, characterized by urate deposits. It has also been presented in other forms of rheumatism, particularly those involving joint affections and sciatica. In acute inflammatory rheumatism cinchophen is a good substitute for salicylates.

Ordinary doses of these compounds seem remarkably safe, and even large amounts cause only temporary poisoning. In a small percentage of cases, however, dangerous toxicity follows even small doses of cinchophen. These "idiosyncrasies" may occur after a few small doses, after long-continued use, or even sometimes after administration has been stopped. The chief danger seems to be an acute hepatitis, and death sometimes follows rather rapidly. To date, nearly 100 deaths have been reported. Under the circumstances no safe method of administration can be outlined; the logical procedure seems to be abandonment of cinchophen. Use of the drug should be terminated promptly on appearance of heartburn, loss of weight, vomiting, diarrhea, albuminuria, hematuria, urticaria, jaundice, or other untoward symptoms. The principal danger at present lies in the numerous proprietary remedies and self-medication by the laity.

Although neocinchophen is probably as effective if given in sufficient amounts, few studies have yet been made, and employment of this substitute should be subject to the same precautions.

3. Colchicum

Colchicum Corm, N.F., B.P. The dried corm of *C. autumnale (Liliaceæ).* Dose: 0.25 Gm., 4 grains, N.F.; maximum 8 grains.

Extract of Colchicum, B.P.

Strong Tincture of Colchicum Corm (Colchicum Wine), N.F. Dose: 0.6 cc., 10 minims, N.F.; maximum 30 minims.

Fluidextract of Colchicum Corm, N.F. Dose: 0.25 cc., 4 minims, N.F.; maximum 8 minims.

Colchicum Seed, U.S.P., B.P. Dose: 0.2 Gm., 3 grains, U.S.P.; maximum 5 grains.

Fluidextract of Colchicum, N.F., B.P. Dose: 0.2 cc., 3 minims, N.F.; maximum 5 minims.

Tincture of Colchicum Seed, U.S.P., B.P. Dose: 2 cc., 30 minims, U.S.P.; maximum 45 minims.

Colchicine, U.S.P. An alkaloid, $C_{22}H_{25}O_6N$, obtained from the seed or corm of colchicum. Dose: 0.0005 Gm., $\frac{1}{120}$ grain, U.S.P.; maximum $\frac{1}{60}$ grain.

Colchicum or its alkaloid, colchicine, has no demonstrable *action* in a therapeutic dose; but if another is then given or a larger one, delayed gastro-intestinal symptoms occur. In still larger amounts the central nervous system is paralyzed in somewhat the same manner as by aconite.

The drug has been used for many years as a *remedy in gout.* If treatment is begun early enough, the pain is promptly relieved, the swelling is reduced in a few days, and the attack lasts but a comparatively short time. Quite frequently, however, no effect at all is obtained, so that some of its former high reputation has been lost. The explanation of its favorable action is still obscure.

One of the chief disadvantages is the danger of *poisoning,* since full doses must be given to obtain the therapeutic effect. The symptoms start in after a delay of several hours, sometimes two or three days, with abdominal pains, vomiting, and diarrhea, accompanied by great prostration. These grow progressively worse, and the central nervous system is probably also paralyzed directly, death finally taking place by failure of the vital functions, without loss of consciousness. In the treatment of gout there is not much danger of fatality, but the exhausting diarrhea and vomiting frequently occur.

4. Lithium

Lithium Bromide, N.F. LiBr. Dose: 1 Gm., 15 grains.
Lithium Carbonate, N.F. Li_2CO_3. Dose: 0.5 Gm., 8 grains.
Lithium Citrate, N.F. $Li_3C_6H_5O_7 \cdot 4H_2O$. Dose: 0.5 Gm., 8 grains.
Lithium Salicylate, N.F. $LiC_7H_5O_3$. Dose: 1 Gm., 15 grains.
Lithium Benzoate, N.F. $LiC_7H_5O_2$. Dose: 1 Gm., 15 grains.
Effervescent Salt of Lithium Citrate, N.F. Dose: 8 Gm., 2 drachms.

Lithium urate is much more soluble than the other salts of uric acid, and it was with the idea of forming it within the body that the compounds of this element were introduced into medicine. This was at a time when the deposition of uric acid was placed as the chief cause of all rheumatisms. It is perfectly obvious to the chemist that no such solution of urate deposits could take place in the presence of sodium and potassium salts, which are omnipresent, yet lithium is still employed in the treatment of these diseases. The carbonate and citrate are alkalizers and diuretics, as are the corresponding salts of other alkali metals, but they are considerably less powerful than those of potassium and more expensive. Lithium resembles the latter in its effects upon the central nervous system.

Mention should be made here of the natural **lithia waters,** once so highly prized by some as remedial agents and still infrequently used. Any virtues certainly cannot be attributed to the lithium content which is minute. In one famous trial it was demonstrated that, in order to get therapeutic doses, one would be obliged to drink 250,000 gallons per day.

Other Antirheumatics

The etiology of various rheumatisms is still obscure, so that no system of medication can be based on absolutely substantial grounds. However, it would seem that alkalizing the body fluids and promotion of diuresis are of great aid, and agents which accomplish these objects are now considered of very great aid in treatment. The antacids and all alkali salts of organic acids, including salicylates, benzoates, citrates, carbonates, and acetates, are universally accepted. Besides these, the alteratives, the bitter tonics, and many other drugs are still prescribed because of time-honored reputation. Piperazine, or diethylene diamine, was once greatly praised as an efficient solvent for urate deposits.

SERUMS AND VACCINES

It is impossible here to review completely the enormous quantity of literature which has accumulated in recent years on this important subject. The number of biological preparations which have been devised and exploited can be conjectured by a careful analysis of those given below, which represents only those that have seemed to be justifiable and for which there is some evidence of value. Hundreds of others have been, or are, available to the practitioner but are undoubtedly and uniformly questionable, some of them frauds.

The manufacture of the products which are used depends upon the ability of animal bodies to elaborate substances which will combat any foreign organism and upon the specific nature of these *antibodies*. When bacteria that are the causative agent in a certain disease are administered to man in attenuated form, by rubbing the latter into a previously prepared abrasion or by injecting subcutaneously, a mild form of the disease is initiated. In an effort to meet this invasion, the body produces a specific antibody in relatively large amount and thus destroys the bacteria. There is thus established an *active immunity*, sufficient to deal effectively with any subsequent inoculation or infection from this particular organism and sometimes adequate for years. Sometimes other animals, usually horses, are utilized to produce these antibodies, which may then be collected and administered to the patient. In such cases there is conferred upon the latter a *passive immunity*, which endures but a short time compared to the active immunity described above. Presumably all pathogenic bacteria, as well as the toxins which they produce, are thus capable of inciting production of antibodies, so that this form of therapy is decidedly important.

The numerous kinds of market preparations, which depend upon the foregoing principles, may be largely placed in two types, the **serums** and vaccines. The former are obtained by filtration from the blood of horses, which have been inoculated with the organism in question or with toxins produced by it, and contain definite antitoxins capable of neutralizing their progenitors. The actual duration of immunity differs markedly for various organisms, because of several factors, and in nearly every case the antibodies are lost or destroyed within a week or two. The **vaccines** are suspensions or extracts of dead bacteria, prepared from animals infected with the disease or collected from the patient himself (autogenous). The immunity conferred by them endures for years in the case of smallpox, a very long time with others, often not at all.

Serums

1. Antitoxins

Diphtheria Antitoxin, U.S.P., B.P. A sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal of the genus *Equus*, which has been immunized against diphtheria toxin. Dose: therapeutic 10,000 units, prophylactic 1000 units, U.S.P.

Tetanus Antitoxin, U.S.P., B.P. As above, from an animal immunized against tetanus toxin. Dose: therapeutic 20,000 units, prophylactic 1500 units, U.S.P.

Scarlet Fever Antitoxin, U.S.P. As above, from an animal immunized against the toxin or toxin-like substance produced by the streptococcus regarded as causative of scarlet fever. Dose: therapeutic 6000 units, prophylactic 2000 units.

Meningococcus Antitoxin, N.R.

Anærobic Antitoxin, N.R., B.P. For treatment of gas gangrene.

Erysipelas Streptococcus Antitoxin, N.R.

Bovine Tetanus Antitoxin, N.R.

Botulinus Antitoxin, N.R.

Bothrops Antitoxin, N.R.

Crotalus Antitoxin, N.R.

The antitoxic **serums** are of *therapeutic value* in a limited number of diseases, best as prophylactics, but also good as curatives. They are standardized against a test dose of toxin, which is, in turn, determined as the largest quantity of the latter that will be neutralized by **one unit** of standard antitoxin, furnished by the U. S. Public Health Service. The potency is thus established for a limited period, but, because it is gradually dissipated, each package of serum is marked with an expiration date, beyond which the product is considered worthless. Keeping in a refrigerator reduces the loss somewhat, and dried serums keep indefinitely, but the latter are difficult to dissolve. Antitoxins for diphtheria and scarlet fever have given nearly perfect results for prevention and often brilliant ones after onset of symptoms; the earlier they are administered the better the chances for recovery. Tetanus antitoxin is uniformly successful to prevent symptoms but is not curative unless enormous doses are introduced into the body by spinal injection. The serums designed for other diseases are less useful, chiefly because of the limited field.

2. Antibacterial Serums

Antimeningococcic Serum, U.S.P. Obtained from the blood of an animal of the genus *Equus* immunized with cultures of the several types of meningococci which prevail in the United States. Dose: 20 cc.

Antipneumococcic Serum, Type I, U.S.P. Obtained from the blood of an animal of the genus *Equus* immunized with cultures of the pneumococcus, type I. Dose: 30 cc.

Antipneumococcic Serum, Type II, N.R.
Antipneumococcic Serum, Types I and II Combined, N.R.
Antidysenteric Serum, N.R., B.P.
Antianthrax Serum, N.R.
Erysipelas Antistreptococcic Serum, N.R.

The antibacterial serums are more complicated and less useful as a class. The greatest success has been found with that for the meningococcus. Type I pneumonia, less so type II, is also effectively treated, but serums against others of the 31 recognized types are inadequate. About half of all pneumonias will be benefited by the serums for types I and II. Others of the antibacterial serums give excellent results at times but are often failures.

3. Convalescent Serums

On theoretical grounds the serum of convalescents should contain antibodies that could be useful against the disease in others. There seems unquestioned evidence that this conclusion is practically valid in scarlet fever and measles; less evidence for infantile paralysis, chicken-pox, mumps, whooping cough, diphtheria, infections by the meningococcus, etc. In epidemics of infantile paralysis, administration of convalescent serum is practically the only therapeutic measure yet available, and many claim that it is specific if given early enough. Pooled normal human serum, which is more easily obtainable, is apparently as successful. The explanation usually given is that many individuals have had light attacks in earlier years. The use of human placenta in measles is probably on the same basis.

Horse Serum

Normal Horse Serum, N.R.

This serum does not contain antibodies and is not used like the others in specific infections. It is said to increase the coagulability of the blood in hemorrhagic conditions, and it is also employed locally in burns and on wounds. Occasionally it has been injected in infectious diseases with alleged success.

Serum Sickness.—When the serums are injected into animals of the same class from which they were prepared, no untoward effects are noted. In man or any other animal, however, there is occasionally a reaction which is called serum sickness, attributable to the foreign proteins and having no connection with the antitoxin; normal horse serum, containing no antibodies, will produce the same result. The symptoms, which consist of skin eruptions, fever, and pains in the joints and muscles, are usually not serious and disappear within a short time. Very rarely, a fatal collapse may take place within a few minutes. These phenomena are probably idiosyncrasies and similar to, perhaps identical with, anaphylaxis which will be discussed later.

Vaccines

These agents for the production of active immunity are undoubtedly useful in medicine. However, the chaotic conditions brought about by the multitude of commercial exploitations has reacted to establish a more or less universal skepticism. Those for smallpox, rabies, and typhoid and the toxoids for scarlet fever and diphtheria are outstanding.

1. Antivirus Vaccines

Smallpox Vaccine, U.S.P., B.P. A glycerinated suspension of the vesicles of vaccinia or cowpox which have been obtained from healthy vaccinated animals of the bovine species.

Rabies Vaccine, U.S.P. A sterile suspension of the attenuated, diluted, dried or dead, fixed virus of rabies.

The success of vaccination against smallpox is one of the shining achievements of modern medicine. The incidence has been reduced from the high figure at the time of Jenner to an almost negligible number in civilized countries today. The small percentage of untoward reactions is insignificant in comparison.

The prophylactic employment of rabies (hydrophobia) vaccine shortly after exposure reduces the mortality to almost zero. The period of incubation is sufficiently long so that immunity is established before the disease appears. A more or less serious paralysis sometimes follows the treatment.

2. Bacterial Vaccines (Bacterins)

Typhoid Vaccine (Enteric Vaccine), U.S.P., B.P. A sterile suspension of killed typhoid bacilli in physiological solution of sodium chloride or other suitable diluent. Dose: 0.5 and 1 cc., the latter dose to be repeated once.

Typhoid and Paratyphoid Vaccine (Mixed Enteric Vaccine), U.S.P., B.P. As above, with an equal amount of paratyphoid bacilli, A and B. Dose: as for typhoid vaccine.

Acne Bacillus Vaccine, N.R.
Cholera Vaccine, N.R.
Plague Bacillus Vaccine, N.R.
Brucella Melitensis Vaccine, N.R.
Staphylococcus Vaccine, N.R.
Erysipelas and Prodigiosus Toxins, N.R.

Therapy by the two typhoid vaccines has been eminently successful in preventing typhoid and paratyphoid fevers, giving an immunity which lasts for two years or longer. As treatment of the diseases or of carriers, they are not believed to be of much service.

The evidence of value for other bacterins is rather inconclusive. Those of plague and cholera are used as prophylactics, while those of acne, brucella (undulant fever), and staphylococcus are employed in treatment, although autogenous vaccines are preferable. The one containing erysipelas and prodigiosus is applied to treating inoperable cancer. Among the numerous other products which have been marketed, several show some promise: whooping cough (pertussis), gonorrhea, colds, etc.

The so-called B.C.G. vaccine for tuberculosis should perhaps be mentioned here. In Europe, and to some extent in this country, thousands of infants have received vaccination by it as a means of conferring immunity for the balance of life. In France at least 20 per cent of the children have been so treated. The claim is made that it protects also against other diseases of childhood, but up to the present very little evidence has been given of value in any respect.

3. Toxins

Diphtheria Toxoid (Anatoxin-Ramon), U.S.P. A sterile aqueous solution of the products of growth of the diphtheria bacillus modified by special treatment. Dose: 1 cc.

Diphtheria Toxin for the Schick Test, U.S.P., B.P. Dose: 0.1 cc.

Diphtheria Toxin-Antitoxin Mixture, N.R., B.P.

Diphtheria Toxoid, Alum Precipitated, N.R.

Scarlet Fever Streptococcus Toxin, U.S.P. A sterile solution in beef broth of certain products including a soluble toxin from suitable strains of hemolytic streptococci.

Tetanus Toxoid, N.R.

Staphylococcus Toxoid, N.R.

The original toxin-antitoxin mixture for diphtheria is successful in conferring immunity, but the toxoids are considered more efficient with children and do not give serum reactions. The immunity lasts for an indefinite time. The use of the toxin (Schick) as diagnostic is thoroughly reliable, so that effectiveness of the immunity can be tested. The toxin of scarlet fever is now employed subcutaneously at weekly intervals to confer active immunity and can also be used in skin tests for effectiveness. There is also some evidence for value of the other toxoids.

4. Tuberculins

Old Tuberculin (Tuberculin-Koch), U.S.P., B.P. A sterile solution in a special liquid culture medium of the soluble products of growth of the tubercle bacillus. Dose: 0.001 cc.

New Tuberculin, N.R.

Tuberculin Denys, N.R.

The official substance is injected as a diagnostic agent, although positive reactions do not necessarily mean active tuberculosis. All three have been employed to prevent or cure the disease. They are certainly not universally effective but may be of some aid.

This is perhaps a good place to discuss the **bacteriophage,** which is produced during the metabolism of certain bacteria and which, as its name indicates, is apparently able to destroy the organism producing it. Furthermore, it is said that the phage can be made specific toward other bacteria by cultural methods. Most of the evidence so far produced has been for the *B. coli* group.

The bacteriophage has been applied as a therapeutic agent in many diseases, and, while there may be some evidence of merit where local application can be made, very little proof is recorded of successful use in disease. The chief deterrent is that its lytic action is apparently ineffective in the presence of colloids, serum, etc.

ALLERGY

Allergenic Extracts, N.R.

Concentrated Pollen Extracts, N.R.

Pollen Allergens Solutions, N.R.

Pollen Antigens, N.R.

Concentrated Pollen Antigens, N.R.

Pollen Extracts, N.R.

Poison Ivy Extract (Ivyol, Rhus Tox. Antigen), N.R. From *Rhus toxicodendron.*

Poison Oak Extract (Ivyol), N.R. From *Rhus diversiloba.*

Rhus Venenata Antigen, N.R.

The injection of a foreign protein by any route other than the oral gives to an animal a *sensitivity* to that protein, which is made evident in a violent reaction during subsequent injections. If the second injection occurs within a few days, there is no great result, but when this period has been extended to 2 weeks, the reaction is usually certain. The sensitization is retained for years and sometimes permanently. The phenomenon, which is called **anaphylaxis**, is unquestionably an observable effect of efforts made by the body to rid itself of the foreign substance and is probably entirely analogous to production of antibodies against bacteria. Common existence of such reactions to food or other materials which are ingested orally would indicate that this sensitization can also be incurred by mouth.

That untoward effects from injection of serums and other biological remedies are manifestations of anaphylaxis seems probable, although some authorities deny this. Very similar are the symptoms of shock after hemorrhage, trauma, or operation. Analogous also are the effects of injecting histamine, peptones, milk, etc.

The symptoms of anaphylaxis will vary somewhat in degree but are usually alike in kind. In the milder forms there is an urticarial eruption of the skin or a swelling of the mucous membranes. In the more severe forms there may also be fall in temperature and blood pressure, violent contractions of unstriated muscles, rapid pulse, respiratory distress, and asphyxia. In some cases the symptoms may come on quickly and severely and may even terminate fatally.

Instances of hypersensitivity to various substances, which are very common, have been called **allergy** and sometimes **atopy.** They are, however, probably manifestations of anaphylaxis; indeed, some authorities consider the three terms synonymous. Allergic reactions to food are increasingly important in therapy, while hay fever and certain forms of asthma and chronic bronchitis also belong in this class.

The **food allergens** and the **pollen extracts** are of value mainly as diagnostic reagents, employed to determine the responsible materials in hay fever, asthma, and other sensitizations. The existence of such conditions is very common, much more so than is usually realized. A large share of the people present a mild or severe reaction to some protein or other. In such case the application of the particular substance to the scarified skin induces a local reaction, in the shape of an urticarial wheal. If the offending protein is then injected periodically in ever increasing doses, the patient is presumed to become *desensitized*, a condition which lasts for a limited time. The treatment of hay fever by this method has been successful in some cases and wholly futile in others. In general the system is not of great value, although very beneficial in particular instances. The best method of treatment of these sensitizations, after determination of identity, is to remove the patient from any opportunity of contact.

Desensitization and treatment in poisoning by the various species of Rhus are attempted by the extracts listed. Although the method has been employed for years, the results are still doubtful. It is probably of little value.

Fever Therapy

The intravenous injection of vaccines or of foreign proteins in general is followed by a fever, muscle and joint pains, sweating, decrease and then increase in leucocytes, and sometimes serious collapse. This has been used therapeutically in the treatment of various infections. The originators hoped (1915) that it would be of service in chronic cases, but most of the value is recorded in acute conditions. The mechanism of action is still obscure, but this "proteotherapy" is generally accepted as a useful system within certain limits. The literature records enthusiastic reports in a host of different diseases, making a critical review rather difficult. However, proteotherapy as the sole method of treatment in any disease is not generally accepted and can be very dangerous. It is presumed to be of some value in acute and chronic arthritis, gonorrhea, certain infections of the skin and eye, a few generalized infections, certain vascular diseases, and cerebrospinal syphilis, especially dementia paralytica.

The means for getting the necessary reaction has altered somewhat during recent years. Originally the substances injected were typhoid and other vaccines, proteose (peptones), milk, etc. Later it was found possible to get similar results with non-protein substances, such as sulfur in oil. Blood serum, urine, and various extracts of tissue (muscle) have been used, and shocks by insulin (*q.v.*) are probably in this class. Since a fever is necessary in the system, inoculations have been made with the organisms of natural fevers, such as malaria and influenza, with even better results in neurosyphilis.

In most recent years external heat is being employed almost exclusively in the large hospitals. This can be produced by short waves or diathermy but preferably by means of an oven. The temperatures recorded are up to 106 or 107°F., and the length of exposure is variable. The results in arthritis, gonorrhea, etc., have been very gratifying.

The injection of venom from snakes, bees, and spiders constitutes another form of fever therapy which is sometimes applied. Snake venom is probably of some value to reduce pain in cancer, neuralgia, sciatica, etc., and to decrease bleeding in hemorrhages, including hemophilia. It is also used as a treatment of epilepsy. The age-old employment of bee stings in rheumatism has led to clinical trials of the venom by injection, but no benefits have yet been shown.

CHAULMOOGRA OIL

Chaulmoogra Oil (Hydnocarpus or Gynocardia Oil), U.S.P., B.P. The fixed oil expressed from the ripe seed of *Taraktogenos Kurzii, Hydnocarpus Wightiana,* or *H. anthelmintica* (*Flacourtiaceæ*). The fixed oil from the seeds of other species of *Hydnocarpus* may be used in its place. Dose: 1 cc., 15 minims, U.S.P.

Ethyl Chaulmoograte (Chaulmestrol), U.S.P., B.P. The ethyl esters of the mixed acids of chaulmoogra oil. Dose: by mouth or by intramuscular injection, 1 cc., 15 minims, U.S.P.

The oil was employed by natives in the treatment of leprosy years before any attention was paid to it by the medical world. Scientific examination recently showed that the oil, the sodium salts of its fatty acids, and esters of the same are *germicidal* in vitro, particularly to acid-fast organisms, and that this property is undoubtedly to be attributed to chaulmoogric acid or to gynocardic or hydnocarpic acids, which may be identical.

The preparations are not specific cures for *leprosy,* because they often fail to be beneficial, but extensive trials under careful control have demonstrated that they frequently exert an excellent influence on the progress of the disease. Indeed, it is probable that cures can be made in early stages, especially of young subjects, and that advanced cases will be improved after sufficient time, unless the disease has progressed beyond a certain point. The drugs are applied locally or given internally in the form of ethyl chaulmoograte. The oil is also recommended as a useful application in tubercular laryngitis, with or without simultaneous medication by lactic acid, and it has been used in lupus, arthritis, and other conditions.

METABOLIC

Strictly speaking, perhaps, any drug is used to affect the metabolism, because this is the total of processes going on within the body, both synthetic and analytic. For convenience, however, we have grouped in this class all those substances which have an influence on indefinite structures or on processes of which we are more or less in ignorance. Each one of them could probably be considered as belonging to the previous class of specifics; notably is this true of insulin, thyroid, iron, and liver.

1. Iron

Iron, U.S.P., B.P. Metallic iron in the form of fine, bright wire.

Reduced Iron, U.S.P., B.P. From ferric oxide by hydrogen. Dose: 0.5 Gm., 8 grains, U.S.P.

Pills of Iron, Quinine, Strychnine and Arsenic (Aitken Tonic Pills), N.F.

Solution of Ferric Chloride, U.S.P., B.P. Dose: 0.1 cc., 1½ minims, U.S.P.

Tincture of Ferric Chloride, U.S.P. Dose: 0.6 cc., 10 minims.

Tincture of Ferric Citrochloride, N.F. Dose: 0.5 cc., 8 minims.

Elixir of Iron, Quinine and Strychnine (Elixir I.Q.S.), N.F. Dose: 4 cc., 1 fluidrachm.

Saccharated Ferric Oxide (Eisenzucker), N.F. Dose: 2 Gm., 30 grains.

Ferrous Sulfate (Copperas, Green Vitriol), U.S.P., B.P. $FeSO_4.7H_2O$. Dose: 0.2 Gm., 3 grains, U.S.P.

Exsiccated Ferrous Sulfate, B.P.

Solution of Ferric Sulfate (Solution of Iron Tersulfate), U.S.P.

Solution of Ferric Subsulfate (Monsel's Solution, Solution of Basic Ferric Sulfate), N.F. Dose: 0.2 cc., 3 minims.

Magma of Ferric Hydroxide (Arsenic Antidote), U.S.P. Dose: 120 cc., 4 fluidounces.

Saccharated Ferrous Carbonate (Saccharated Iron Carbonate), N.F., B.P. Dose: 0.25 Gm., 4 grains, N.F.

Pills of Ferrous Carbonate (Chalybeate Pills, Blaud's Pills, Ferruginous Pills), U.S.P., B.P.

Mass of Ferrous Carbonate (Vallet's Mass), U.S.P. Dose: 0.25 Gm., 4 grains.

Solution of Iron and Ammonium Acetate (Basham's Mixture), N.F. Dose: 15 cc., 4 fluidrachms.

Soluble Ferric Phosphate, N.F. Ferric phosphate rendered soluble by the presence of sodium citrate. Dose: 0.25 Gm., 4 grains.

Elixir of Iron, Quinine and Strychnine Phosphates, N.F. Dose: 4 cc., 1 fluidrachm.

Syrup of Iron, Quinine and Strychnine Phosphates (Easton's Syrup), B.P.

Compound Syrup of Ferrous Phosphate, B.P.

Soluble Ferric Pyrophosphate, N.F. Dose: 0.25 Gm., 4 grains.

Iron and Ammonium Citrates (Ammonio-ferric Citrate), U.S.P., B.P. Ferric citrate rendered more readily soluble by the presence of ammonium citrate. Dose: 2 Gm., 30 grains, U.S.P.

Green Iron and Ammonium Citrates, U.S.P. Dose: parenteral 0.06 Gm., 1 grain.

Ampuls of Green Iron and Ammonium Citrates, N.F. Dose: 1 cc. (0.1 Gm.).

Iron and Quinine Citrate, B.P.

Ferrous Lactate (Iron Lactate), N.R. Dose: 0.06 to 1.3 Gm.

Injection of Iron, B.P.

Peptonized Iron (Iron Peptonate), N.F. A compound of iron oxide and peptone, rendered soluble by the presence of sodium citrate. Dose: 0.3 Gm., 5 grains.

Solution of Peptonized Iron, N.F. Dose: 8 cc., 2 fluidrachms.

Solution of Peptonized Iron and Manganese, N.F. Dose: 8 cc., 2 fluidrachms.

The element iron is a constant component of most plant and animal organisms and presumably essential to their existence. In the *human body* most of it exists as hemoglobin of the blood, but all organs and tissues, and probably all cells, contain it in small amounts. The same condition holds true for other animals. Even those whose blood contains none are dependent on iron in most other portions of the anatomy. It apparently is essential to chlorophyl formation in plants although not contained in the pigment itself, and it is a constant factor in many enzymes especially the oxidases.

The *bodily equilibrium* during conditions of variable intake is maintained by storage and changed excretion. The total amount in human beings is about 2.5 to 3.5 grams, nearly 85 per cent of which is in the hemoglobin. During the processes of metabolism, a portion of the tissues and blood is continually being destroyed, freeing some iron and eliminating 5 to 20 milligrams per day, chiefly by the feces but also by the urine. This is balanced by intake from food which usually supplies about 15 milligrams daily. If the diet should be enriched by larger quantities, the excess may be stored to some extent, but most of it passes through to be ejected at the rectum. The unrequired compounds which are absorbed are transported by the blood to the spleen, where they undergo uncertain changes in structure and shortly after are distributed to the liver and bone marrow, mostly to the former. A majority may remain as reserve in the liver, less in the spleen and marrow, but the rest is slowly excreted through the cecal and colonic epithelium into the feces. The amount in the urine and bile is altered but little by changes in intake. The oral administration of iron compounds has no other effect than does an extra amount in the food. A large share is unabsorbed, and the remainder follows the usual route to the spleen and liver and to final excretion at the colon.

There has been a great deal of debate as to whether *organic* or *masked* iron is not alone absorbed and utilized by the organism. These terms are applied to the substances which do not give iron reactions, such as ammonia or hydrogen sulfide precipitation, in contradistinction to *inorganic* which do, even if the iron in the latter is linked to an acidic radical of carbon, like that of acetic acid. Without relating any details of experimentation and discussion, which went on for years, it may be sufficient to state that no difference in absorption and fate is now generally conceded. The inorganic iron is just as utilizable as any other form and may even have an advantage.

The therapeutic administration of iron compounds produces *little apparent effect.* The salts precipitate protein and are thus irritating and astringent, but this action is not sufficient to cause much protoplasmic poisoning. If the combination is with strong acids, the anion is the predominating factor, so that substances like ferric chloride are sufficiently corrosive to produce gastro-enteritis. A prolonged ingestion of milder salts may give rise to digestive disturbances because of interference with normal peptic and tryptic actions and also because of continued hyperacidity of the stomach. Usually, however, the iron follows the normal route of partial absorption without any striking effect. There may be some influences on the processes of metabolism, because iron is a component of all tissues, but, if so, this does not become apparent. Hypodermic injection of inorganic compounds gives severe local inflammation, which may be serious, and which can be eliminated by using the masked forms. Intravenous or subcutaneous administration of the latter in large doses causes direct systemic poisoning, similar to that of arsenic, but in therapeutic amounts no notable action.

The chief use of iron in medicine is as *hematinic,* or tonic to the blood. There may be many other functions of iron in the metabolism which could be utilized if they were understood, but the value as component of the blood is the only one clearly recognized. Without an adequate supply of the element there could be certainly no replacement or increment of hemoglobin, and there is some evidence to indicate that it also stimulates the blood-making organs. It is, therefore, administered under conditions of anemia, in the simple form produced by hemorrhage or operation, where much blood has been lost, and in chlorosis, characterized by reduction in hemoglobin, but in which the pathology and etiology are little understood. The clinical results in these conditions are sometimes brilliant and usually good. In pernicious anemia, iron is probably worthless. In addition to the hematinic value, iron may perform the functions of a stomachic, increasing appetite and the amount of digestive juices, and thus aid in treatment. It is often prescribed during convalescence from acute disease and in the run-down conditions after malaria and other chronic maladies.

The *minor uses* of iron salts are becoming less and less important. The crude sulfate is sometimes added to sewage or industrial water to disinfect, which it does by mechanically precipitating protein. The chloride was formerly regarded as an efficient astringent and hemostatic and is still an ingredient of mouthwashes and applied on bleeding surfaces. The Jacobi mixture, with potassium chlorate, which produces some chlorine, was once very popular.

The iron used internally for its hematinic value may be in almost *any form.* As was explained above, the older idea that organic compounds alone are efficient was found to be erroneous. In general, the carbonate as Blaud's pills is probably the most useful preparation. In fact it is difficult to see why there should be so many official forms of the element. The doses of any of them are certainly more than enough, usually, and could be reduced without detriment. Those combinations designed for hypodermic injection have probably no more effect than the same amount of others by mouth, but this is by no means a settled question, and iron is often given by the needle route.

2. Phosphorus

Phosphorus, N.F. The yellow allotropic form of the element phosphorus. Dose: 0.0006 Gm., 1/100 grain; maximum 1/25 grain.

Phosphorated Oil, N.F. Dose: 0.06 cc., 1 minim.

Elixir of Phosphorus, N.F. Dose: 4 cc., 1 fluidrachm.

This element is an important *constituent of animal cells,* comprising somewhat less than 1 per cent of the human body. It is especially concentrated in the nerve and brain cells but also in significant amounts in the bones, muscles, and bloodstream. The functions attached to phosphorus are undoubtedly essential but, in spite of extensive and numerous investigations, are not well understood. During the ordinary processes of metabolism, about 1.5 grams are excreted daily, which is readily made up by the diet. In case the amount in the latter is too small, the deficit could easily be furnished by administration of any phosphorus compound, because all the necessary compounds are synthesized from inorganic phosphates, and any other form is first transformed to the latter. As a matter of fact, however, there is probably never any deficiency in phosphorus intake. Any diseases which might be attributed to such lack are due to failure in utilizing the supply.

Because of its insolubility in water, phosphorus is very slowly *absorbed* from the intestinal tract, whether it is in the form of solid or as solution in fats. It is taken up to some extent by inhalation of the vapor. Its *fate* in the body has not been determined with certainty, but it is known to inhibit the action of oxidizing ferments, and, from the effects in poisoning, it is presumed to be distributed extensively and very slowly changed to inorganic phosphates.

The therapeutic administration is followed by numerous and wide *effects* on the metabolism and tissues, about which little is known. The chief effect is, apparently, a stimulation of bone formation, particularly in youth where the bones are in process of growth. Although many authorities have observed such results, it must be admitted that there are recorded many instances of negative effects and that the descriptions of positive ones often present disagreements. Another result of the administration seems to be a proliferation of the interstitial connective tissue of liver, kidney, and alimentary walls, which ultimately produces an inflammation of these organs. Fatty degeneration of many parts, including muscular tissue, probably results from protein destruction, which also leads to extensive changes in composition of blood, urine, and other fluids. The nervous system is not appreciably affected by therapeutic doses and apparently never directly.

The presumable action on bony structure is utilized in several diseases characterized by poor formation or growth, such as *rickets,* dental caries, and osteomalacia. The administration must be continued for long periods in doses of about 1 milligram per day, given at meals in the form of pills or of solution in oil. The evidence for value is contradictory, and there is always great danger of toxic effects. Phosphorus has also been suggested and used in various *nervous diseases,* anemias, sexual atonia, etc., mostly because of long practice and with no positive evidence of merit.

Acute poisoning may occur from matches, rat poisons, overdosage, or industrial accidents. Infusion of matches has been known to be used as abortifacient. Death has resulted from 1 grain, but about twice this amount is generally required; ⅓ grain may give severe symptoms. The mortality is very high, at least half being fatal, and some authorities state that recovery is rare.

The *symptoms* are encountered in two well-defined stages. The first effects which are observed are those of gastro-intestinal irritation, including pain, eructations of a garlic odor, vomiting, and often diarrhea. After a time there is more or less complete remission for two or three days, when the second stage begins, with the same symptoms over again in exaggerated form. Blood may accompany the vomit and stools, and there may be some jaundice. If death does not occur within a short time, the jaundice becomes more severe, while anxiety, muscular pains, headache, and scanty urine are added. There may also be multiple hemorrhages from the skin, mucous membranes, lungs, bladder, etc. The pulse gradually becomes weaker, and the respiration very irregular, and death takes place from failure of the latter, usually before consciousness is lost. If the patient should recover from the direct poisoning, general paralysis is often encountered as a permanent result.

Treatment consists in eliminating the poison from the alimentary tract and in systemic measures. Copper sulfate has been used as an antidote on the theory that it will form the phosphide of copper, and also because it is an emetic. In any event it would appear to be harmless. Potassium permanganate (0.1 per cent), solution of hydrogen peroxide, or dilute solutions of other oxidizing agents may be used to wash out the stomach. Old oil of turpentine is presumed to form a molecular, insoluble compound and is often tried, but it is probably useless and may be harmful in assisting absorption. After the stomach is thoroughly washed out, a saline cathartic may be administered, and sodium carbonate or bicarbonate to prevent acidosis. Milk, oils, fats, etc., must be avoided at all times. If the systemic effects have started, the further treatment is merely symptomatic. Blood transfusions have been tried and seem to have given good results in some cases.

Chronic poisoning is of considerable, but decreasing, interest in the arts and occasionally is encountered in therapy. The effects are necrosis of the jaw bone, emaciation, and sometimes respiratory diseases. Sanitary, dietary, and prophylactic measures must be strictly observed, the aid of surgery being also frequently necessary.

3. Phosphorus Compounds

Calcium Glycerophosphate, N.F. $CaPO_4C_3H_5(OH)_2$. Dose: 0.3 Gm., 5 grains.

Sodium Glycerophosphate, N.F. $Na_2PO_4C_3H_5(OH)_2$. Dose: 0.25 Gm., 4 grains.

Ferric Glycerophosphate, N.F. Dose: 0.2 Gm., 3 grains.

Manganese Glycerophosphate, N.F. Dose: 0.2 Gm., 3 grains.

Elixir of Calcium and Sodium Glycerophosphates, N.F. Dose: 4 cc., 1 fluidrachm.

Compound Elixir of Glycerophosphates (Compound Solution of Glycerophosphates), N.F. Dose: 8 cc., 2 fluidrachms.

Hypophosphorous Acid, U.S.P., B.P. An aqueous solution containing 30 to 32 per cent of HPH_2O_2. Dose: 0.2 cc., 3 minims, U.S.P.

Dilute Hypophosphorous Acid, B.P. 10 per cent.

Sodium Hypophosphite, N.F., B.P. $NaPH_2O_2.\ H_2O$. Dose: 0.5 Gm., 8 grains, N.F.

Potassium Hypophosphite, N.F. KPH_2O_2. Dose: 0.5 Gm., 8 grains.

Ammonium Hypophosphite, N.F. $NH_4PH_2O_2$. Dose: 0.2 Gm., 3 grains.

Calcium Hypophosphite, N.F., B.P. $Ca(PH_2O_2)_2$. Dose: 0.5 Gm., 8 grains, N.F.

Ferric Hypophosphite, N.F. $Fe(PH_2O_2)_3$. Dose: 0.2 Gm., 3 grains.

Manganese Hypophosphite, N.F. $Mn(PH_2O_2)_2 \cdot H_2O$. Dose: 0.2 Gm., 3 grains.

Syrup of Hypophosphites, N.F. Dose: 8 cc., 2 fluidrachms.

Compound Syrup of Hypophosphites, N.F. Dose: 8 cc., 2 fluidrachms.

Syrup of Ammonium Hypophosphite, N.F. Dose: 4 cc., 1 fluidrachm.

The **hypophosphites** were introduced in 1855 for the treatment of tuberculosis, in the belief that this disease is caused by lack of oxidation, which they might stimulate. No satisfactory evidence has ever been presented to show that they have any effect on nutrition or metabolism in general. They are absorbed as such and excreted practically unchanged. While they have been abandoned in tuberculosis, they still have a large use in conditions characterized by malnutrition, anemia, and emaciation. The compound syrup, containing as it does quinine and strychnine, may be of some value as a stomachic under such circumstances, but the hypophosphites themselves are probably worthless.

The **glycerophosphates** are employed for the same purposes, in the belief that they furnish lecithin, which is a component of many body cells, chiefly those of the brain and nerves. The administration of lecithins was presumed to stimulate the formation of red blood corpuscles and to promote growth and nutrition. There is some unconfirmed evidence to substantiate this point of view, but the decomposition after absorption, and the fact that organic phosphorus compounds are built up from the inorganic, would tend to discredit any beneficial action. Although no one has yet proved it, the glycerophosphates, being part of the lecithin molecule, are supposed to be more easily formed into the latter. The calcium salt is generally preferred, because of its properties and because the metabolism of calcium and phosphorus is intimately interrelated. As a matter of fact, the salt is decomposed to phosphoric acid and glycerin, the first being excreted and the second oxidized, so that it is probably no better than a mixture of glycerin and inorganic phosphates.

4. Radiotherapy

Thorium Nitrate, N.R. $Th(NO_3)_4 \cdot 4H_2O$.

In spite of the wonderful progress which has already been made in the knowledge of *radioactivity* and its accompaniments, it is certain that we have by no means reached the end. Since its discovery by Becquerel in 1896, those metals which give off radiations have been studied by thousands of investigators with eminently satisfactory results. The real stimulus to the rapid development which has ensued has rested in the recognition of radium by the Curies in 1898, in the later disclosures that its radiations are exceptionally powerful, and in the discovery that some, if not all, of the emanations are identical with those from the Roentgen tube, including X-rays. A review of the history of this progress during the following 30 years is undoubtedly as vivid and colorful a romance as was ever written. The weirdness of atomic decay, the enormous amount of energy which is thus liberated, and the almost supernatural penetrability are without eclipse in the story of science. Yet there is undoubtedly much to be learned about these discoveries, especially in connection with their utilitarian value.

When an electric discharge is sent between poles in a highly evacuated tube, rays of radiant matter emanate from both electrodes, called cathode and anode rays, respectively. The former, impinging on glass, render it fluorescent, and they also raise the temperature of objects in their path, produce many chemical changes, cause a fog in moist air, and pass through thin sheets of metals. When they strike glass or other surfaces, they are transformed into an entirely different form, the *X- or Roentgen-ray.* The latter rays pass through glass and other solid matter, are not deflected by a magnet, and are capable of producing photographs. In contact with barium, tungsten, or zinc salts they produce a fluorescence.

Certain elements, either free or as salts, are continuously giving off radiations, similar to the ones produced electrically. Those from **radium,** which is the only one active enough to be useful, are mixtures of three rays, alpha, beta, and gamma, in the proportion of 90, 9, and 1, respectively. The alpha rays, which are very similar to those from the anode of the Roentgen tube, are quickly stopped by solid substances, and even by air, being then discharged and converted to helium. The beta rays are identical with those from the cathode, while the gamma rays are produced by the impact of the beta on surrounding matter. The production of energy from radium amounts to about 120 calories per hour per gram of radium.

If the skin is exposed to a radioactive substance, there is produced a *local action* varying, with the amount and length of exposure, from a slight erythema by stimulation to an extensive ulceration. The depth to which the effect penetrates can be controlled to some extent by regulating the exposure and by the use of metal filters. Although there has been some difference in the clinical findings with radium and with Roentgen rays, the general action is clearly similar. The former has the advantage that it is usable in many cases where the latter would be mechanically inoperable. The dose is usually stated in milligram-hours of exposure, but there are various other means of expression.

It is obviously impossible to give a detailed account of those diseases which can be cured or alleviated by *radiotherapy* and of the methods for applying; a brief summary must suffice. There is good evidence that the rays are remedial or curative of a number of conditions characterized by abnormal tissue, such as various sarcomas, chronic eczema, and rodent ulcer, and of considerable benefit in psoriasis, leukoplakia, exophthalmic goiter, carcinoma of the breast, etc. The greatest value is shown in cancers, whose tissues seem to be particularly susceptible to the rays, and it is notable that radium or X-ray will sometimes cure such a condition which is beyond surgical help, also that the rays are of immense aid to surgery before and after operations on cancer. The general effects of the radiations on the metabolism are not well understood, but they are certainly of great value in the treatment of several diseases.

The *emanation* (radon) is an inert gas which is actively radiating, in the same way as the parent substance. It can be collected and purified and then administered in metal capsules, in water solution, or inhaled as produced. Any substance exposed to it receives an active deposit which can also be used. The effect produced by any of these products is exactly the same as if radium itself were employed, but all of them quickly lose their activity, while the metal is almost inexhaustible.

In spite of early hopes to make this emanation of great value in medicine, application of it today is very limited. Certain it is that the various types of apparatus designed to give activated preparations are without value and are sometimes dangerous. The extravagant claims made for them are certainly to be condemned.

Thorium and **uranium** compounds are also fairly active, but therapeutic use of this property is almost lacking. Thorium nitrate has been applied locally in cancer, and the emanation is sometimes inhaled in tuberculosis. Employment of the colloidal oxide as an X-ray contrast medium has been found to be dangerous. Uranium nitrate was formerly used as an antiseptic without advantage and with considerable danger.

Sunlight is a mixture of visible and invisible rays which are much longer than the gamma or X-ray. It is certainly important as aid in treatment of disease, chiefly because of its short, invisible rays, the ultraviolet. The longer, infra-red, rays of sunlight, which are practically only sources of heat, are unimportant. While artificial radiations have largely usurped the place of sunlight in medicine, the latter is still an influential factor in the treatment of many conditions.

Ultraviolet radiations, which are contained in sunlight to a limited extent, can be manufactured easily by a number of electrical methods and with a variety of wave-lengths. The effects of application to the body are similar to those from X-ray but weaker. That they are powerful, however, can easily be appreciated by recognizing that sunburn and snow blindness are caused by the small quantity of ultraviolet in ordinary sunlight. They are employed to kill micro-organisms in skin diseases, localized infections, etc., and to disinfect water for swimming pools and for drinking. They are also applied for the metabolic effects in a great variety of diseases, often with brilliant results, and also too frequently with no evidence of value. Use in rickets and similar conditions or to produce antirachitic substances has already been discussed under vitamin D and cod liver oil.

The *promiscuous use* and sale of lamps is fraught with grave *dangers* and should be condemned. A skilled operator and careful regulation of dosage are absolutely necessary, if one is to prevent serious burns. One who has been afflicted with a blistering sunburn can imagine what would be the effect if this were greatly magnified. Furthermore, it is absolutely necessary to make a correct diagnosis before using the light, because it is decidedly harmful to some conditions, and there are narrow limits to its value in others.

ENDOCRINES AND RELATED SUBSTANCES

The endocrines, or glands of internal secretion, constitute a very complicated and interrelated system in the animal body. Those which are recognized clearly are the thyroid, suprarenals, pituitary, pancreas, parathyroid, and gonads. In addition, the thymus, pineal, spleen, and other organs may belong in this class. While the liver and stomach are not endocrinal, they are placed here for convenience.

It is now clearly recognized that the system is intimately concerned with the processes of metabolism and with probably all actions that go on within the body. The functions performed by these glands are apparently dependent in entirety upon their internal secretions (incretions). Each of the latter contains one or more potent principles called **hormones,** some of which have been isolated and studied extensively. In some cases we have some knowledge of how they bring about their important effects, but in the majority the mechanism can only be conjectured. From what is known we can assume that the hormones act in a manifold way and that the whole endocrine system involves a very intricate network of interdependence and correlation.

Since our knowledge of mechanism and function is so limited, it is not hard to understand that therapeutic applications of the hormones is somewhat limited. Epinephrine, insulin, pituitary, and thyroid have a restricted role, although a useful one, in our armamentarium, perhaps also the principles from parathyroid, suprarenal cortex, and gonads, but it is certain that further knowledge can enlarge the field many times. At present much of the therapy with glandular products is empirical, unsatisfactory, and often chaotic.

1. Thyroid

Thyroid, U.S.P., B.P. The cleaned, dried, and powdered thyroid gland, previously deprived of connective tissue and fat, obtained from domesticated animals that are used for food by man. Dose: 0.06 Gm., 1 grain, U.S.P.; maximum 5 grains.

Thyroxin, U.S.P. $C_6H_2(OH)I_2{\cdot}O{\cdot}C_6H_2I_2{\cdot}CH_2{\cdot}CH(NH_2)COOH$. An active physiological principle obtained from the thyroid gland or prepared synthetically. Contains not less than 64 per cent of iodine. Dose: 0.0005 Gm., $\frac{1}{120}$ grain.

Synthetic Thyroxine, N.R.

Thyroxine Crude, N.R. For oral use only.

This gland is intimately concerned with basal metabolism, regulation of growth and development, reproduction, and probably other processes. It secretes, among other iodine compounds, thyroxin, which probably constitutes a large percentage of its activity.

Absence or lack of functioning leads to a fairly well-defined syndrome which is called myxedema or, if congenital, cretinism. The main effects are retardation of growth and mental development, dermal edema, rough and dry hair, and anemia. Simple or colloid goiter is probably caused by defective functioning of the gland, while other types of goiter are associated with alterations of the thyroid in some way.

Hyperthyroidism, brought about by increased activity or by administration, produces very marked results. After a single dose of thyroxin they do not appear for a day or two, reach the maximum in 10 days, and continue for up to 3 weeks. There is a very high basal metabolism, with increased excretion of nitrogen and consumption of oxygen; a great increase in appetite; and loss of weight. The toxic symptoms are restlessness, nervousness, headache, insomnia, muscular weakness, indefinite pains, sweating, rapid heart with palpitation, tremors of the extremities, glycosuria, diarrhea, anemia, and emaciation.

Where there is a lack of secretion, as in myxedema and cretinism, administration of thyroid may be considered specific. Thyroxin will accomplish the same purpose but is proportionately less active. Divided doses are better than single large ones, and the amount must be small at first to avoid delayed toxicity. It is also essential that determinations of the basal metabolism be made periodically. Therapy is also indicated in simple goiter where iodides will usually bring reduction just as well and are much cheaper. Thyroid seems to have a favorable influence on the healing of fractures and is given in obstinate cases of delayed union. It has also been administered in nephrosis or nephritis with edema, in some forms of rheumatism, in skin diseases such as in alopecia areata, etc.

The most common application of thyroid today is in obesity. Without doubt, excessive obesity can be readily reduced by this means, but there is very great danger. Without careful adherence to diet, ingestion of the gland will accomplish little, and, with such adherence, it is seldom needed. The intelligent physician uses thyroid preparations only in selected cases and rarely if the basal metabolism is normal or high. The numerous commercial preparations present grave dangers and should be prohibited.

2. Pituitary

Posterior Pituitary (Hypophysis Sicca), U.S.P. The cleaned, dried, and powdered posterior lobe obtained from the pituitary body of domesticated animals which are used for food by man.

Solution of Posterior Pituitary (Pituitrin), U.S.P., B.P. Dose: 1 cc., 15 minims, hypodermic, U.S.P.

Ampuls of Posterior Pituitary, N.F. Dose: 1 cc.

Ampuls of Pitocin, N.R.

Ampuls of Pitressin, N.R.

Whole Pituitary, N.F. Dose: 0.06 Gm., 1 grain.

Anterior Pituitary, N.F. Dose: 0.3 Gm., 5 grains.

The posterior portion has received most attention up to recent years, although it is not essential to life, while the anterior part is. The respective functions are apparently distinct but possibly interdependent. The posterior secretion has been separated into two fractions, pitocin or oxytocin and pitressin or vasopressin.

Locally applied, extracts of the posterior lobe cause some constriction, mildly like that of epinephrine. Physiologic effects are not produced after oral administration because of destruction by the digestive enzymes; they follow hypodermic, intranasal, or rectal administration. The chief effect is a widespread stimulation of smooth muscle by direct action. The muscles affected are those of the uterus, bladder, blood vessels, intestines, and lacteal glands. The blood pressure is not altered unless full doses have been given intravenously, when there is a rise which is less than that from epinephrine but lasts longer. The heart is slowed and weakened, and the respiration is depressed after reflex stimulation. The urinary output is temporarily increased and then greatly decreased, especially if it has been abnormally high. The secretion of milk is temporarily accelerated without changing the ultimate daily output. Pituitary extract is antagonistic to insulin and counteracts shock by the latter.

The extract is used intramuscularly as a stimulant to the uterine muscle in conditions in which this is atonic and to prevent postpartum and other uterine hemorrhages. As is the case with ergot, there is great differences of opinion as to whether it should be used during the early stages of labor, but many claim that it is perfectly safe if the dosage is regulated and of great advantage. The extract has been injected intravenously in shock and other conditions of low blood pressure and subcutaneously for atonic states of the vesical or intestinal muscles, especially in the characteristic paralysis of these after operation and in enuresis. The excessive diuresis of diabetes insipidus is efficiently reduced after several injections of pituitary, although this can be but temporary. The extract is presumably remedial also in pyelitis, herpes zoster, ureteral calculi, gastric ulcer, etc., and it is sometimes a substitute for epinephrine as addition to local anesthetics. Pitocin may have the uterine action with little effect on the other muscles, while pitressin may be used for vascular stimulation free from oxytocic effects.

Overdoses of the drug give no important toxicity except in pregnancy, where there may be considerable danger. It is, however, not an abortifacient.

The **anterior** lobe is apparently an exceedingly important link in the endocrine system and probably the most complicated. Experimental results would indicate that it is the activating force for some, if not all, of the glands of internal secretion. It thus possesses several separate activities, each of which may be due to a distinctly different hormone: (1) a growth factor which regulates bodily development; (2) prolan A which induces formation of the ovarian follicle; (3) prolan B which stimulates formation of the corpus luteum; (4) prolactin which promotes lactation; (5) a ketogenic factor increasing ketone bodies in the blood; (6) a diabetogenic substance antagonistic to insulin; (7) a stimulator of thyroid development and activity; (8) a factor stimulating the parathyroids; (9) one activating the adrenal cortex; (10) one which induces ovulation. The gonadotropic substance which is obtained from the urine of pregnancy, and which is assumed to come from the pituitary, possibly originates in the placenta. It forms the basis of much used tests for pregnancy.

In the light of the confused state of knowledge in regard to the anterior lobe, it is not surprising that therapeutic applications are rather indefinite and more or less empirical. By mouth it probably has no useful action except in large doses. Whenever there is a deficiency of the hormones, naturally administration by injection would be indicated, but there is no agreement on the specific symptoms which show the lack. However, the gland is called specific in adiposogenital dystrophy which is usually considered a sign of poor functioning, although careful extirpation does not always lead to this disease. It is also administered for undeveloped sex characteristics, undescended testes, delayed puberty; various menstrual disorders; alopecia areata; myasthenia gravis; acne; etc. In all of these it is still considered experimental.

3. Pancreas

Insulin (Iletin), N.R. An aqueous solution of an active principle from the pancreas which affects sugar metabolism.

Protamine Zinc Insulin, N.R.

It has been known for nearly fifty years that the pancreas is intimately concerned with the utilization of sugar and that extirpation of the gland gives a dangerous hyperglycemia. Attempts to isolate in usable form the principle responsible for its normal activity were unsuccessful until 1921 when Banting and Best produced insulin from the portion known as the island of Langerhans. Later Abel succeeded in separating the pure principle in the crystalline state and found it very like proteins. It is ineffective orally because it is destroyed by the digestive juices, but after injection it gives a lowering of blood sugar whether this is previously normal or not. The strength is expressed in units, eight of which are equivalent to 1 milligram of a standard preparation of insulin hydrochloride or to an amount necessary to give definite lowering of sugar in a stated time.

Therapeutically insulin is practically specific in diabetic coma and acidosis, since the disease is apparently caused by deficiency in functioning of the pancreas. For diabetics who cannot be kept symptom-free through dietary measures, insulin is prescribed in amounts determined by careful study. It is not a cure but sometimes may be withdrawn as the islands recover their normal activity. Overdoses give rise to severe poisoning known as insulin shock. The symptoms are weakness, nervousness, rapid pulse, sweating, acute distress with mental disturbance, excitement, vertigo, delirium, convulsions, collapse. These may be counteracted by orange juice or dextrose orally, by the latter intravenously, or if there is an emergency by the subcutaneous injection of epinephrine and oral administration of the carbohydrate.

Protamine and zinc stabilize and prolong the effects of insulin in such a way that the blood sugar can be kept normal 24 hours a day. The main value of the combination is in moderate cases of diabetes.

Insulin is administrated also in non-diabetic conditions, often with dextrose or a surplus of food. Those for which there is clinical evidence are acidosis after operation or labor, vomiting of children and pregnancy, and the undernutrition of psychoneuroses, tuberculosis, some heart diseases, convalescence, etc. It has also been employed in pruritus, pernicious anemia, gastric ulcers, arthritis, menstrual disorders, and others. The shock of overdoses is claimed to be of great benefit in some cases of dementia praecox, sometimes in other types of mental disease, but the danger of toxicity necessitates careful dosage.

Several guanidine derivatives have the power to reduce blood sugar as insulin has, but this is weaker, and the danger of poisoning is much greater. Synthalin and synthalin-B are still sometimes prescribed.

An insulin-free extract of pancreas is said to contain a substance that will reduce blood pressure; it has been administered in angina pectoris with reported success.

4. Parathyroid

Solution of Parathyroid (Parathyroid Extract, Paroidin), U.S.P. Solution of the water-soluble principles of fresh parathyroid glands of healthy domesticated animals used for food by man. Dose: hypodermic 25 units.

The only known function of the gland is control of blood calcium. Injection of the solution, but not oral ingestion, gives an increase, 100 units producing in normal dogs a rise of 1 milligram per 100 cubic centimeters within 16 to 18 hours. This is gradually reduced to normal after 20 to 24 hours. Together with the increase in calcium there is also a higher value for its excretion in the urine and for that of phosphates. Repeated injections of the solution give less and less effect.

The solution is specific, even if only temporary, in the tetany caused by removal of the gland or by disease and apparently also in infantile tetany. The success in these has brought about trials in gastric tetany, chorea, and similar conditions, but the clinical evidence is meager. Combined with administration of calcium, the solution may be indicated whenever content of the former in the blood is low, a condition found in a number of diseases. Overdoses can easily give symptoms of poisoning which may become very serious, and any therapeutic use should involve careful checks of blood calcium.

5. Suprarenal

Suprarenal (Adrenals), N.F. The dried, partially defatted and powdered suprarenal gland of cattle, sheep, or hogs. Dose: 0.25 Gm., 4 grains.

Adrenal Cortex Extract (Cortin), N.R.

The medullary portion furnishes epinephrine which has already been discussed, but it is not essential to existence, as is the cortical part. Removal of the latter brings about severe symptoms and death in a few days. Addison's disease, in which the effects are similar, is presumed to be caused by suprarenal insufficiency. Oral ingestion of the dried gland, however, gives no improvement in the disease and will not sustain life in an animal from which the organ has been removed. Injection of the specially prepared extract, on the other hand, is able to supply the deficiency for apparently an indefinite time. Application of this in Addison's disease has given improvement in the majority of cases, some of them permanent, although the treatment is expensive. The failures emphasize that the extract is not entirely specific. Trials have been made in other nervous diseases and conditions of asthenia, in myasthenia gravis, etc. Announcement of its remedial value in cancer a few years ago appeared to be entirely without foundation.

6. Gonads

Ovary, N.F. The dried, undefatted, and powdered ovary of cattle, sheep, or swine. Dose: 0.3 Gm., 5 grains.

Ovarian Residue, N.F. The ovary without the corpus luteum. Dose: 0.3 Gm., 5 grains.

Corpus Luteum, N.F. Dose: 0.3 Gm., 5 grains.

Perhaps there has been no chapter in endocrinal investigation so replete with confusion and yet so rich in definite results as that concerned with the gonads. From the maze of conflicting data no attempt can be made here to record a complete survey of the voluminous literature. We can only here summarize what seems to be the status today.

Incited by the two important hormones of the anterior pituitary, the ovary produces several active substances, some of which have been isolated and carefully studied. The exact function possessed by each is more or less conjectural, but some of the effects are very definite. Attempts to use the ovary or extracts by the oral route have produced practically negative results, and it is concluded that oral therapy with ovarian preparations is useless.

Estrone (**theelin,** folliculin, amniotin, female sex hormone, etc.) seems to originate in the ovarian follicle, although the latter contains very little. It is presumed to promote growth of tubes, uterus, and vagina in the immature, as well as the secondary sex characteristics. In the mature it induces estrus, prepares the uterus for menstruation, and activates the endometrium to the effects of the luteal hormone. It is also said to promote formation of tumors. Its potency is measured by ability to produce estrus in rats or mice. Other estrogenic substances which have been prepared are estradiol (dihydrotheelin) which is even more active, estriol (theelol), estrane, estranol, estranediol, estratriene, estrenol, equilin, and equilenin.

Progesterone (progestin, corporin, luteosterone), arising in the corpus luteum, is closely allied to these chemically. It is apparently concerned with preparation of the uterus for implantation and nutrition of the ovum. It is present only in menstruation or pregnancy.

Therapeutic applications of these substances are not yet well defined. Estrone is employed by injection in amenorrhea, dysmenorrhea, symptoms of the menopause, functional sterility, and other reproductive disorders. It has also been recommended in hemophilia and other hemorrhagic conditions, to prevent conception and terminate pregnancy, in anemia, epilepsy, arthritis, etc. Progesterone is injected for habitual or threatened abortion and for menstrual bleeding or pain.

Extracts of the placenta (immune globulin) have given some promise in preventing infectious diseases, especially in measles and scarlet fever. This, however, is presumed to be independent of hormones.

Testicular extracts, when given by injection, are known to have stimulating effects on the secondary sex characteristics. They have not yet been successfully used in therapy in spite of claims for value in impotence. The **male sex hormone** has been isolated and found chemically similar to estrogenic substances. It can be estimated qualitatively and quantitatively by growth of a cockscomb and by other methods.

Other Endocrines

The thymus gland, which is large at birth, gradually becomes smaller in later life. Whether it gives an internal secretion is not known, and no definite function is actually proved. Attempts to utilize in therapy to hasten growth and reproduction and in the healing of fractures have met with little success.

Just as little is known about the pineal gland, although some suspect that it is endocrinal and closely associated with growth and sex. The claims that heart, kidneys, lachrymal glands, lymph glands, etc., secrete hormones are certainly not proved. The spleen will probably function temporarily as an activator of calcium when the parathyroid is diseased, but little success has attended efforts to use extracts in tuberculosis and conditions where the blood is abnormal.

7. Liver and Stomach

Extract of Liver, U.S.P. A soluble fraction of mammalian livers which increases the red blood corpuscles in pernicious anemia.

Solution of Liver, U.S.P.

Purified Solution of Liver (Parental Solution of Liver), U.S.P.

Ventriculin, N.R. Desiccated, defatted hog stomach.

Extralin, N.R. A concentrate from liver and stomach.

Daily ingestion of adequate amounts of liver or stomach tissues will induce and maintain remission of pernicious anemia and sprue when the diseases have not progressed too far. Other animal organs give the same effects in larger doses. The responsible substance may be enzymatic or hormonal. The strength of a preparation is judged by the reticulocyte response in a patient with pernicious anemia. Intramuscular or intravenous injection of suitable extracts will accomplish the same purpose and has advantages in rapidity and where a diet of liver or stomach is objectionable. The dose required varies up to a pound of fresh liver per day. Liver is also said to have diuretic, detoxifying, anticoagulant, antiscorbutic, hypotensive, and insulin-like properties. It has been recommended in other anemias, eclampsia, diabetes, skin diseases, high blood pressure, edemas, sclerosis, pellagra, etc., but there is not sufficient evidence of value in most cases.

Powdered gastric **mucin** from the stomach of hogs is administered orally for the relief of symptoms in gastro-duodenal ulcers. It is presumed to cause this effect by absorbing hydrochloric acid and thus protecting the mucosa.

8. Aminoacids

Aminoacetic Acid (Glycine, Glycocoll), N.R. $NH_2 \cdot CH_2 \cdot COOH$. Dose: 20 to 30 Gm. daily.

In myasthenia gravis or progressive muscular dystrophy the daily ingestion of glycine gives improvement and diminution of symptoms in many cases. It is said that reduction in the characteristic fatigue can also be utilized in this same feature of other diseases. Ephedrine, which is itself used in myasthenia, is sometimes given with the glycine. Glutamic acid may be substituted for glycine but presents no advantage.

Histidine hydrochloride (larostidin) is employed intramuscularly (2 to 5 cubic centimeters of 4 per cent solution) in peptic ulcer, for which it may be useful. Tryptophane has been applied in the same way. Both histidine and cysteine are sometimes used for the local treatment of ulcers.

IMPORTANT POISONS NOT USED AS DRUGS

1. Methyl Alcohol

Methyl or wood alcohol, being largely employed as a denaturant of grain spirit and also as a solvent in the arts, is frequently a cause of poisoning. The systemic effects are very similar to those from ordinary alcohol, with more local irritation and muscular weakness and a coma which is more profound and prolonged. In general, it is less toxic in single dose, but repeated ones seem to give a greater effect, possibly because of lessened ability of the tissues to produce oxidation. The greatest danger from wood alcohol, however, lies in the tendency to total and permanent blindness by atrophy of the optic nerve, a condition which is frequently the sequel. The treatment in acute poisoning would be identical with that for ethyl alcohol.

2. Amyl Alcohol

In the production of ethyl alcohol by fermentation, a mixture of amyl alcohols, or fusel oil, is always formed in small amount, so that most alcoholic beverages contain some. In whiskies properly prepared, most of this has been removed, but in the moonshines so common in this country, the fusel oil is retained. Nevertheless, it is seldom that this can be blamed for poisoning in alcoholism, regardless of popular impressions to the contrary; in order to get toxic amounts, it would be necessary to ingest much more than a fatal dose of ethyl alcohol, which is about one-fourth as potent. The effects, however, are entirely analogous, with more nausea and vomiting from local action and a more persistent coma. The treatment is also as for poisoning by ethyl alcohol.

3. Carbon Monoxide

This compound is the potent ingredient of illuminating and water gas, which are so often the cause of accidental or suicidal poisonings. The effects are due to the prevention of oxygenation of the blood and thus terminate in a typical asphyxia. The symptoms are headache, dizziness, muscular debility, rapid pulse, drowsiness, unconsciousness, noisy breathing, some cyanosis of the external mucosa and extremities, gradual weakening of the heart and respiration, with finally a deep coma, possibly tetanic convulsions. The blood retains a bright-red color, even after being treated with reducing agents, a fact of the greatest diagnostic importance. If the patient is revived, there may be a long period of convalescence and great tendency to various complicating diseases.

The *treatment* is usually successful if life still exists, and if the remedial measures are carried out with enough persistence. The poisonous effects are caused entirely by the union of the poison with the blood to form carbon monoxide hemoglobin, this being possible because the affinity for hemoglobin is about two hundred times that of oxygen, which is displaced, therefore, whenever the gas is present in the inspired air. Thus, the aim of resuscitation must be to supplant the poison with oxygen, by giving the latter under pressure, usually mixed with some carbon dioxide. In the absence of these substances, artificial respiration may be completely effective and, in the lighter cases, simply fresh air. If the poisoning has been very severe, it may be necessary to make a transfusion of blood from a healthy person. The patient must be carefully protected from draughts and cold for several days or weeks.

4. Nitric Oxide

When nitric acid acts as an oxidizing agent, which it does in contact with most metals and practically all organic materials, there is given off a mixture of gases, chiefly nitric oxide and nitrogen peroxide. These are very irritating to the mucous membranes during exposure, but the effects disappear as soon as the offending gases have been removed. Some time afterward, however, the individual may experience rapid bronchitis and pulmonary edema, which are frequently fatal within two or three days. Sometimes the voice is completely lost for a year or more, until the patient finally succumbs to respiratory disease. Great caution must be observed in handling or breathing any compounds which would be liable to give such vapors. In case this is necessary, the nose and mouth should be protected with a moistened sponge, preferably with soda solution, or by means of a gas mask.

5. Sulfur Dioxide

Sulfur dioxide is very irritating to mucous membranes because of general protoplasmic poisoning by reduction. Inhaled in low concentration, it causes tingling in the nose and bronchi and, in larger amounts, inflammation of the entire respiratory tract, with sneezing, coughing, tears, inability to breathe, asphyxia, and rapid death; 1:100,000 is irritating, and 1:1000 is quickly fatal. Bacteria also are killed by sufficient concentrations of the gas, a fact which is still utilized in the disinfection of rooms by filling with gas from a tank or by burning 3 pounds of sulfur per 1000 cubic feet. The practical value of the method is very limited, and sulfur dioxide has now been practically abandoned in favor of formaldehyde. The chief disadvantage is in corrosion of metals and rotting of fabrics.

In case of poisoning, the toxic effects are best treated by fresh air and artificial respiration if necessary. The cautious inhalation of ammonia may serve as a means of curtailing the action.

6. Oxalic Acid

Oxalic acid is of interest chiefly because it is sometimes mistaken for crystals of similar appearance. Poisoning by it is almost always accidental. The fatal dose is presumably about 2 drachms. The most important effects are due to its general precipitation of calcium in the bodily tissues, but it is also locally irritating like other acids. A case can easily be distinguished from one due to mineral acids by the rapidity with which the toxicity progresses. Oxalic acid has been known to cause death in a very few minutes. The symptoms are primarily those of gastro-enteritis, chiefly vomiting, with an early collapse and finally paralysis of the respiration, but there may also be convulsions. Calcium salts of any kind are efficient antidotes for the unabsorbed portion, and calcium lactate by intravenous injection has been recommended for that in the circulation. The balance of treatment would consist in stimulants, such as digitalis or strophanthin and caffeine.

7. Food Poisonings

The development of *ptomaines,* which are usually simple amines, by the decomposition of foods is not nearly so common as was formerly supposed when all kinds of toxicity from food was termed ptomaine poisoning. In fact such substances are probably the result of diseased conditions in animals used for food and are comparatively rare. No attempt can be made here to detail the various forms of poisonings experienced by ingestion of tainted foods, since they are of great variety, as would be expected when one considers the infinite number of possible compounds that could be produced. The symptoms may present almost any pathological condition and must be treated accordingly.

One kind, which is sharply distinguished from the rest, is **botulism,** a form of toxicity attributable to *Bacillus botulinus* or rather to a toxin developed by that organism. The latter grows only under anærobic conditions, such as are found in canned goods and tightly enclosed foods, and is quite easily affected by heat and reagents. The spores, however, are very resistant, so that when raw materials which contain them are subjected to the usual sterilization process, especially in home canning, the spores are unaffected and later develop within the can. Since the evidences of this growth are often readily apparent when the cans are opened, by the appearance of bad odor and excess gas, such food should be destroyed. The toxin, which is extremely virulent, can easily be destroyed by boiling for 30 minutes or less, and, since the spores are harmless, such a procedure is ample security.

The *symptoms,* which appear in 12 to 24 hours, consist in nausea, vomiting, dizziness, abdominal pain, difficulty in speech and swallowing, derangement of special senses, and respiratory failure. Death generally occurs within 24 hours after onset but may be delayed much longer. The only treatment which has given any encouragement is by means of an antitoxin. The chief difficulty has always been to get the serum from the nearest available point in sufficient time.

APPENDIX

I. Posology

(A list of average and maximum doses for the common drugs.)

The following table gives the maximum and average doses of those drugs for which dosage is important. In order to save space, there are omitted all those whose maximum dose is one drachm or more, the less important preparations of the British Pharmacopœia, most of the volatile oils, and all fluidextracts. Doses of the last named may be taken as equal to those of the crude drugs from which they are derived. The most important substances are marked with an asterisk, and the student will be expected to learn the doses of these. The metric figures are given in grams or cubic centimeters, and the Apothecaries' measures are in grains or minims. The doses are oral unless otherwise stated.

	Maximum		Average	
	Metric	Apoth	Metric	Apoth
*Acetanilid	0.5		0.02	3
Acetanilid compound powder	0.75	12	0.3	5
Acetarsone	0.5	8	0.25	4
*Acetophenetidin	1.0	15	0.3	5
Acetylsalicylic acid	1.2	20	0.3	5
Acetyltannic acid	2.0	30	0.6	10
*Aconite	0.12	2	0.06	1
*Aconite tincture	1.0	15	0.6	10
Adonis	0.6	10	0.125	2
Afenil	3.0	45	1.0	15
Aloe	0.6	10	0.25	4
Aloe extract	0.5	8	0.12	2
Aloin	0.12	2	0.015	¼
Aluminum chloride	1.0	15	0.3	5
Alurate and sodium salt	0.5	8	0.1	1½

	Maximum		Average	
	Metric	Apoth.	Metric	Apoth
*Aminopyrine	1.0	15	0.3	5
*Ammonia water	2.0	30	1.0	15
Ammonia anisated spirit	2.0	30	1.0	15
Ammonia aromatic spirit	4.0	60	2.0	30
Ammonium benzoate	2.0	30	1.0	15
Ammonium bromide	2.0	30	1.0	15
*Ammonium carbonate	0.6	10	0.3	5
*Ammonium chloride	1.2	20	1.0	15
Ammonium hypophosphite	1.0	15	0.2	3
Ammonium iodide	1.0	15	0.3	5
*Ammonium salicylate	2.0	30	1.0	15
Ammonium valerate	0.3	5	0.125	2
*Amyl nitrite	0.3	5	0.2	3
Amytal and sodium salt	1.0	15	0.3	5
Anethol	0.3	5	0.1	1½
Anise	2.0	30	0.5	8
Anise spirit	3.0	45	1.0	15
*Antimony and potassium tartrate	0.06	1	0.003	1/20
Antimony tincture	3.0	45	1.0	15
*Antipyrine	1.0	15	0.3	5
Apocynum	1.0	15	0.2	3
*Apomorphine hydrochloride	0.015	¼	0.001	1/60
Arbutin	1.0	15	0.3	5
Arnica	0.3	5	0.2	3
Arnica tincture	3.0	45	1.0	15
*Arsenic trioxide	0.006	1/10	0.002	1/30
*Arsenous acid solution	0.6	10	0.2	3
*Arsenous iodide	0.012	1/5	0.005	1/12
*Arsenous and mercuric iodide solution	0.6	10	0.1	1½
Arsphenamine intravenous	0.4	6	0.4	6
Arsphenamine silver intravenous	0.5	8	0.3	5
Asafetida	1.2	20	0.4	6
*Aspidium oleoresin	4.0	60	4.0	60
*Atropine salts	0.001	1/60	0.0005	1/120
*Barbital and sodium salt	1.0	15	0.3	5
*Belladonna leaf	0.2	3	0.06	1
*Belladonna extract	0.06	1	0.015	¼
*Belladonna tincture	2.0	30	0.6	10
*Belladonna root	0.2	3	0.045	¾
Benzaldehyde	0.12	2	0.03	½